Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

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Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

7E12

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

5/4/10

9/28/10

Point of Contact:
Technical Info. Specialist
CM1 12C14 Tel: 306-4504

****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable
Searcher: _____	NA Sequence (#)_____		STN _____
Searcher Phone #: _____	AA Sequence (#)_____		Dialog _____
Searcher Location: _____	Structure (#)	_____	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic	_____	Dr.Link _____
Date Completed: _____	Litigation	_____	Lexis/Nexis_____
Searcher Prep & Review Time: _____	Fulltext	_____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family	_____	WWW/Internet _____
Online Time: _____	Other	_____	Other (specify)_____

PTO-1590 (1-2000)

McCaa
09/715172

FILE 'REGISTRY' ENTERED AT 14:38:23 ON 23 APR 2001

STRUCTURE FILE UPDATES: 22 APR 2001 HIGHEST RN 332014-61-6
DICTIONARY FILE UPDATES: 22 APR 2001 HIGHEST RN 332014-61-6

TSCA INFORMATION NOW CURRENT THROUGH January 11, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON MEDULLASIN/CN

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 9004-06-2 REGISTRY
CN Elastase (9CI) (CA INDEX NAME)
OTHER NAMES:
CN E.C. 3.4.21.11
CN E.C. 3.4.21.36
CN E.C. 3.4.21.37
CN E.C. 3.4.24.65
CN E.C. 3.4.4.7
CN Elastase 2
CN Elaszym
CN Macrophage metalloelastase
CN Matrix metalloproteinase-12
CN **Medullasin**
CN MMP 12
CN Neutrophil Elastase
CN Pancreatopeptidase E
CN Peptidase, pancreato-, E
CN Proteinase, bone marrow serine
DR 9001-21-2, 139074-64-9, 75603-19-9, 83682-98-8
MF Unspecified
CI COM, MAN
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MRCK*, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Searcher : Shears 308-4994

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
6431 REFERENCES IN FILE CA (1967 TO DATE)
241 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6440 REFERENCES IN FILE CAPLUS (1967 TO DATE)

FILE 'CAPLUS' ENTERED AT 14:38:24 ON 23 APR 2001

FILE COVERS 1947 - 23 Apr 2001 VOL 134 ISS 18
FILE LAST UPDATED: 22 Apr 2001 (20010422/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

CAplus now provides online access to patents and literature covered in CA from 1947 to the present. On April 22, 2001 bibliographic information and abstracts were added for over 2.2 million references published in CA from 1947 to 1966.

The CA Lexicon is now available in the Controlled Term (/CT) field. Enter HELP LEXICON for full details.

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON MEDULLASIN/CN
L2 9904 SEA FILE=CAPLUS ABB=ON PLU=ON L1 OR MEDULLASIN OR ELASTASE OR (MATRIX(W)(METALLOPROTEINASE OR METALLO PROTEINASE))(2A)12
L7 13 SEA FILE=CAPLUS ABB=ON PLU=ON L2 AND (MULTIPLE SCLER? OR MS(S)SCLER?)

L7 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:730142 CAPLUS
DOCUMENT NUMBER: 134:204585
TITLE: Determination of **medullasin** levels for the diagnosis of **multiple sclerosis**
AUTHOR(S): Aoki, Y.; Saida, T.; Nakano, I.; Saito, T.; Ikeguchi, K.; Urabe, T.; Nishiguchi, E.; Suzuki, H.; Takahashi, K.; Katsuragi, H.; Mizuno, Y.
CORPORATE SOURCE: Faculty of Human Life Sciences, Jissen Women's University, Tokyo, 191-8510, Japan
SOURCE: Acta Neurol. Scand. (2000), 102(4), 218-221
CODEN: ANRSAS; ISSN: 0001-6314
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To obtain a simple and reliable clin. parameter for the diagnosis of **multiple sclerosis** among patients with neurol. diseases. Heparinized peripheral blood was obtained from patients with **multiple sclerosis** and those with noninflammatory neurol. diseases and healthy volunteers. A new enzyme immunoassay method detg. meduallasin levels in human granulocytes was developed by using mouse monoclonal antibody against **medullasin**. A newly developed enzyme immunoassay method for **medullasin** can detect as little as 1 ng/mL **medullasin** and results can be obtained within 2 h. Eighty-five out of 112 patients with **multiple sclerosis** (75.8%) showed pos. results (above means of normals + 2 SD) in the **medullasin** test, while 15.4% (12/78) of patients with non-inflammatory neurol. disease had pos. results. This newly developed enzyme immunoassay method for **medullasin** is considered to be a useful paraclin. test for the diagnosis of **multiple sclerosis**.

IT **9004-06-2, Medullasin**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of **medullasin** levels for diagnosis of **multiple sclerosis**)

REFERENCE COUNT: 11
REFERENCE(S):
(2) Aoki, Y; Arthritis Rheum 1983, V26, P1002 CAPLUS
(3) Aoki, Y; Clin Chim Acta 1988, V178, P193 CAPLUS
(5) Aoki, Y; J Biol Chem 1978, V253, P2026 CAPLUS
(6) Aoki, Y; J Clin Invest 1982, V69, P1223 CAPLUS
(8) Ishikawa, E; J Immunoassay 1983, V4, P209 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:688272 CAPLUS
DOCUMENT NUMBER: 133:280563
TITLE: Human antibodies that bind human IL-12 and methods for producing
INVENTOR(S): Salfeld, Jochen G.; Roguska, Michael; Paskind, Michael; Banerjee, Subhashis; Tracey, Daniel E.; White, Michael; Kaymakcalan, Zehra; Labkovsky, Boris; Sakorafas, Paul; Friedrich, Stuart; Myles, Angela; Veldman, Geertruida M.; Venturini, Amy; Warne, Nicholas W.; Widom, Angela; Elvin, John G.; Duncan, Alexander R.; Derbyshire, Elaine J.; Carmen, Sara; Smith, Stephen; Holtet, Thor Las; Du, Fou Sarah L.
PATENT ASSIGNEE(S): Basf A.-G., Germany; Genetics Institute Inc.; et al.
SOURCE: PCT Int. Appl., 377 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056772	A1	20000928	WO 2000-US7946	20000324

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-126603 P 19990325

AB Human antibodies, preferably recombinant human antibodies, that specifically bind to human interleukin-12 (hIL-12) are disclosed. Preferred antibodies have high affinity for hIL-12 and neutralize hIL-12 activity in vitro and in vivo . An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. The antibodies, or antibody portions, of the invention are useful for detecting hIL-12 and for inhibiting hIL-12 activity, e.g., in a human subject suffering from a disorder in which hIL-12 activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant human antibodies of the invention, and methods of

synthesizing the recombinant human antibodies, are also encompassed by the invention.

IT **9004-06-2, Elastase**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; recombinant human antibodies that bind human IL-12 for treatment of autoimmune diseases and inflammatory diseases)

REFERENCE COUNT: 7
REFERENCE(S):
(2) Carter, R; HYBRIDOMA 1997, V16(4), P363 CAPLUS
(3) Genentech Inc; WO 9404679 A 1994 CAPLUS
(4) Genetics Inst; WO 9524918 A 1995 CAPLUS
(5) Irving, R; IMMUNOTECHNOLOGY 1996, V2(2), P127 CAPLUS
(6) Pini, A; JOURNAL OF IMMUNOLOGICAL METHODS 1997, V206(1-2), P171 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:628008 CAPLUS
DOCUMENT NUMBER: 133:217724
TITLE: Inhibitors of serine protease activity, and methods and compositions for treatment of nitric oxide-induced clinical conditions
INVENTOR(S): Shapiro, Leland
PATENT ASSIGNEE(S): The Trustees of University Technology Corp., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051623	A2	20000908	WO 2000-US5556	20000303
WO 2000051623	A3	20001214		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-123167 P 19990305
US 1999-156523 P 19990929

AB A method of treating and preventing diseases is provided. In particular, compns. and methods of blocking diseases assocd. with aberrant levels of nitric oxide and facilitated by a serine proteolytic activity are disclosed, which consist of administering to a subject a therapeutically effective amt. of a compd. having a serine protease inhibitory activity. Among effective compds. are .alpha.1-antitrypsin and synthetic drugs mimicking some or all of the actions of .alpha.1-antitrypsin.

IT **9004-06-2, Elastase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; serine protease inhibitors for treatment of NO-induced diseases)

L7 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:144905 CAPLUS
DOCUMENT NUMBER: 132:206953
TITLE: Anti-inflammatory peptides derived from IL-2 and analogues thereof
INVENTOR(S): Lider, Ofer; Ariel, Amiram; Hershkoviz, Rami; Yavin, Eran J.; Fridkin, Matityahu
PATENT ASSIGNEE(S): Yeda Research and Development Co. Ltd., Israel
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000011028	A2	20000302	WO 1999-IL448	19990819
WO 2000011028	A3	20000706		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9953002	A1	20000314	AU 1999-53002	19990819

PRIORITY APPLN. INFO.:

GB 1998-18370	A	19980821
IL 1998-126009	A	19980831
IL 1999-129980	A	19990516
WO 1999-IL448	W	19990819

AB Synthetic anti-inflammatory peptides derived from the sequence of IL-2 are provided. Parent peptides of the sequences Ile-Val-Leu,

Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr and Arg-Met-Leu-Thr, were obtained by **elastase** enzymic digestion of IL-2, synthesized and modified. The peptides are useful in conditions of acute and chronic inflammation such as in autoimmune diseases.

IT **9004-06-2, Elastase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IL-2-derived peptides and analogs for treating inflammation and autoimmune disease)

L7 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:361718 CAPLUS
DOCUMENT NUMBER: 131:43586
TITLE: Preparation of anti-human **medullasin** monoclonal antibody for immunoassay
INVENTOR(S): Aoki, Yosuke; Suzuki, Hideaki; Takahashi, Shigeyoshi; Katsuragi, Hisashi
PATENT ASSIGNEE(S): Dainichi Seika Kogyo K. K., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11151085	A2	19990608	JP 1997-336303	19971120

AB Provided is an IgG-type mouse monoclonal antibody to human **medullasin**, a serine protease in granulocytes. **Medullasin** prepd. from human granulocytes was used to immunize BALB/c mice and the immunized spleen cells were fused with mouse P3-X63-Ag8-U1 (P3U1) myeloma cells to prep. hybridoma cells secreting the monoclonal antibody. Use of the monoclonal antibody for immunoassay of **medullasin** during clin. diagnosis of chronic inflammatory diseases or **multiple sclerosis** was shown.

IT **83682-98-8, Medullasin**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(prepn. of anti-human **medullasin** monoclonal antibody for immunoassay)

L7 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:325911 CAPLUS
DOCUMENT NUMBER: 130:347431
TITLE: Compounds which inhibit tryptase activity, and use in the treatment and prevention of inflammatory disease

INVENTOR(S): Burgess, Laurence; Rizzi, James P.
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9924407	A1	19990520	WO 1998-US23362	19981103
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9912089	A1	19990531	AU 1999-12089	19981103
EP 1030844	A1	20000830	EP 1998-955238	19981103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1997-65154 P 19971110
US 1998-179695 A 19981027
WO 1998-US23362 W 19981103

OTHER SOURCE(S): MARPAT 130:347431

AB Compds. are provided which are capable of inhibiting the activity of tryptase. Such compds. are useful in the treatment or prevention of inflammatory disease, particularly those disease states which are mediated by mast cell activation. Also provided are formulations comprising the noted compds., processes for prepg. such compds., and methods for treating or preventing an inflammatory disease.

IT **9004-06-2, Elastase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(tryptase inhibitors and use in treatment and prevention of inflammatory disease)

REFERENCE COUNT: 14
REFERENCE(S):
(1) Anon; WO 9420527 A CAPLUS
(2) Arris Pharmaceutical Corp; WO 9609297 A 1996 CAPLUS
(3) Boehringer Mannheim GMBH; WO 9427958 A 1994 CAPLUS
(4) Daiichi Pharmaceutical Co, Ltd; EP 0540051 A 1993 CAPLUS

(5) Du Pont Merck Pharmaceutical Co; WO 9801428 A 1998 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:172616 CAPLUS
DOCUMENT NUMBER: 130:208821
TITLE: A process for inhibiting complement activation via the alternative pathway
INVENTOR(S): Gupta-Bansal, Rekha; Brunden, Kurt R.; Parent, James B.
PATENT ASSIGNEE(S): Gliatech Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910009	A1	19990304	WO 1998-US17500	19980824
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9892033	A1	19990316	AU 1998-92033	19980824
EP 1007092	A1	20000614	EP 1998-944501	19980824
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO 2000000935	A	20000418	NO 2000-935	20000225

PRIORITY APPLN. INFO.: US 1997-918349 A 19970826
WO 1998-US17500 W 19980824

AB A process for inhibiting activation of complement via the alternative pathway, including inhibiting the formation of complement activation products via the alternative pathway, is provided. Monoclonal anti-properdin antibody is used to inhibit properdin-induced stabilization of C3 convertase and binding of properdin to C3b for inhibiting complement activation. The antibody is useful in treating acute or chronic condition such as myocardial infarction, acute respiratory distress syndrome, burn injury, stroke, pancreatitis, cardiopulmonary bypass, ischemia/reperfusion injury, **multiple sclerosis**, rheumatoid

arthritis, myasthenia gravis or Alzheimer's disease.

IT **9004-06-2D, Elastase**, antitrypsin complex
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(monoclonal anti-properdin antibody for inhibition of C3 convertase stabilization, C3b binding and complement activation and for treatment of acute injury and chronic disease such as **multiple sclerosis**)

REFERENCE COUNT: 5
REFERENCE(S):
(1) Alexion Pharaceuticals Inc; WO 9525540 A 1995 CAPLUS
(2) Fearon, D; THE JOURNAL OF EXPERIMENTAL MEDICINE 1980, V152(1), P20 CAPLUS
(3) Gonzalez-Rubio, C; THE JOURNAL OF BIOLOGICAL CHEMISTRY 1994, V269(42), P26017 CAPLUS
(4) Huemer, H; IMMUNOLOGY 1993, V79(4), P639 CAPLUS
(5) Whiteman, L; THE JOURNAL OF IMMUNOLOGY 1991, V147(4), P1344 CAPLUS

L7 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:394241 CAPLUS
DOCUMENT NUMBER: 129:62957
TITLE: Inhibitors of invasive tissue remodelling for use as contraceptives and antitumor agents
INVENTOR(S): Lund, Leif Roge; Dano, Keld; Stephens, Ross; Brunner, Nils; Solberg, Helene; Holst-Hansen, Claus; Nielsen, John Romer
PATENT ASSIGNEE(S): Fonden Til Fremme Af Eksperimentel Cancerforskning, Den.; Dano, Keld; Stephens, Ross; Brunner, Nils; Solberg, Helene; Holst-Hansen, Claus; Nielsen, John Romer
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9824474	A1	19980611	WO 1997-DK555	19971208

W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,

FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9851876	A1	19980629	AU 1998-51876	19971208
EP 942746	A1	19990922	EP 1997-946746	19971208

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.:	DK 1996-1402	19961206
	WO 1997-DK555	19971208

AB The invention pertains to novel methods for preventing or arresting invasive remodelling in mammals by utilising a combination of in vivo inhibition of plasmin and in vivo inhibition of certain other proteolytic enzymes, notably metalloproteases. The method can e.g. be used as a novel alternative to current methods of contraception as well as antifungal and antibacterial treatment. The preferred embodiments relate to treatment and prevention of neoplastic diseases by use of these combinations. Further, the invention relates to novel compns. which comprises a plasmin inhibitor in admixt. with an inhibitor of another proteolytic enzyme, preferably an inhibitor of a metalloprotease.

IT **9004-06-2, Elastase**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(inhibitors; inhibitors of invasive tissue remodelling for use as contraceptives and antitumor agents)

L7 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	1998:380778 CAPLUS
DOCUMENT NUMBER:	129:121080
TITLE:	Matrix metalloproteinase expression in an experimentally-induced DTH model of **multiple sclerosis** in the rat CNS
AUTHOR(S):	Anthony, D. C.; Miller, K. M.; Fearn, S.; Townsend, M. J.; Wells, G. M. A.; Clements, J. M.; Chandler, S.; Gearing, A. J. H.; Perry, V. H.
CORPORATE SOURCE:	Department of Pharmacology, The CNS Inflammation Group, University of Oxford, Oxford, OX1 3QT, UK
SOURCE:	J. Neuroimmunol. (1998), 87(1,2), 62-72 CODEN: JNRIDW; ISSN: 0165-5728
PUBLISHER:	Elsevier Science B.V.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB In an exptl.-induced DTH model of MS, we examd. mRNA and protein expression of a range of MMPs and of TNF.alpha. to establish the contribution that individual MMPs might make to the pathogenesis. In control rat brain, mRNA for all of the MMPs examd. was

detectable. However, by immunohistochem., only MMP-2 could be detected. In the DTH lesions, significant increases in the level of mRNA expression were obsd. for MMP-7, MMP-8, MMP-12, and TNF.alpha.. Where expression of MMP mRNA was increased, there was a corresponding increase in protein expression detected by immunohistochem. To det. whether the upregulated MMPs could invoke destructive events in the CNS, highly purified activated MMP-7, MMP-8, and MMP-9 were stereotaxically injected into the brain parenchyma. All provoked recruitment of leukocytes and BBB breakdown. In addn., MMPs 7 and 9 induced loss of myelin staining. In conclusion, specific MMPs are upregulated in DTH lesions; for the most part, measurement of mRNA was a predictor of increased protein expression. From our injections of MMPs, it is clear that the upregulated MMPs in the DTH lesions could participate in the disruption of the BBB, leukocyte recruitment, and tissue damage.

IT **9004-06-2, Matrix metalloproteinase-12**

RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)

(**matrix metalloproteinase** expression in exptl.-induced DTH model of **multiple sclerosis** in rat central nervous system)

L7 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:197516 CAPLUS

DOCUMENT NUMBER: 128:270870

TITLE: Preparation of 3-mercaptoacetylamino-1,5-substituted-2-azepinone derivatives as matrix metalloproteinase inhibitors

INVENTOR(S): Warshawsky, Alan M.; Flynn, Gary A.; Patel, Meena V.; Beight, Douglas W.; Burkhart, Joseph P.; Tsay, Jiu-Tsair; Janusz, Michael J.; Shen, Jian; Dharanipragada, Ramalinga M.

PATENT ASSIGNEE(S): Hoechst Marion Roussel, Inc., USA

SOURCE: PCT Int. Appl., 160 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9812211	A1	19980326	WO 1997-US13738	19970804

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,

TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9738278	A1	19980414	AU 1997-38278	19970804	
AU 718055	B2	20000406			
EP 928291	A1	19990714	EP 1997-935308	19970804	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
CN 1234039	A	19991103	CN 1997-199024	19970804	
BR 9713207	A	20000404	BR 1997-13207	19970804	
JP 2001501926	T2	20010213	JP 1998-514658	19970804	
NO 9901316	A	19990518	NO 1999-1316	19990318	
PRIORITY APPLN. INFO.:			US 1996-719291	A	19960919
			WO 1997-US13738	W	19970804

OTHER SOURCE(S): MARPAT 128:270870
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to certain novel title compds. I [R1 = C1-6 alkyl, W-(CH2)m, Q-Z-(CH2)m; W = phthalimido; Z = bond, O, NR6, CONR6, NR6CO, NHCONR6, O2CNR6, NHCO2, SO2NR6; Q = H, Y-(CH2)n; Y = H, C6-10 aryl, C3-9 heteroaryl, CO2R6, NR62, morpholino, piperidino, pyrrolidino, isoindolyl; R2 = C1-4 alkyl, (CH2)p-(C3-9) heteroaryl, (CH2)p-Ar1; Ar1 = (un)substituted Ph or naphthyl; R3 = H, C1-6 alkyl, CH2SCH2NHAc, (CH2)p-A, (CH2)m-B, CH2-D-R7; A = C6-10 aryl, C3-9 heteroaryl, cyclohexyl; B = NR72, guanidino, nitroguanidino, CO2R6, CONR6; D = O, S; R4 = H, (CH2)m-S(O)pX1(R6)2; R5 = H, C1-6 alkyl; NR4R5 = piperidino, pyrrolidino, isoindolyl; R6 = H, C1-6 alkyl; R7 = H, C1-4 alkyl, (CH2)p-Ar1; R8 = H, CO2R7, CO(CH2)q-K, S-G; K = nitrogen-contg. heterocycle, NR9R10; G = substituted alkyl; R9, R10 = independently C1-4 alkyl, (CH2)p-Ar1; X, X1 = independently CH, N; m = 2-4; n = 0-4; p = 0-2; q = 0-5] as matrix metalloproteinase inhibitors. Pharmaceutical compns. contg. said compds. as well as methods of treating various disease states responding to inhibition of matrix metalloproteinase are also claimed herein. Thus, reductive alkylation of H-L-Phe-NHMe.HCl with azido aldehyde II (prepd. in 5 steps from 4-phenylcyclohexanone), followed by deesterification and cyclization gave cis azepine III and its corresponding trans isomer in a 4:5 ratio. Redn. of III with 1,3-propanedithiol gave the corresponding amine, which was coupled with 2-bromo-6-phthalimidohexanoic acid to give bromide IV (R = Br). Substitution of IV (R = Br) with p-methoxybenzyl

mercaptan followed by deprotection gave title compd. IV (R = SH) (MDL 108,180). MDL 108,180 inhibited matrix metalloproteinases MMP-2, MMP-3, and MMP-12 in vitro with Ki = 1.2 nM, 39 nM, and 18 nM, resp.

IT **9004-06-2, Matrix metalloproteinase-12**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. of substituted (mercaptoacetylamino)azepinone derivs. as matrix metalloproteinase inhibitors)

L7 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:163608 CAPLUS
DOCUMENT NUMBER: 128:227064
TITLE: Cloning, sequence, and expression of multifunctional enzyme isoform genes from krill
INVENTOR(S): Kay, John; Kille, Peter
PATENT ASSIGNEE(S): Phairson Medical, Inc., UK; Kay, John; Kille, Peter
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808863	A1	19980305	WO 1997-US15179	19970828
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6040155	A	20000321	US 1996-705875	19960828
CA 2259151	AA	19980305	CA 1997-2259151	19970828
AU 9741679	A1	19980319	AU 1997-41679	19970828
GB 2329896	A1	19990407	GB 1998-28022	19970828
EP 925307	A1	19990630	EP 1997-939637	19970828
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001500373	T2	20010116	JP 1998-511922	19970828
DK 9900148	A	19990204	DK 1999-148	19990204

PRIORITY APPLN. INFO.: US 1996-705875 A 19960828

US 1996-768318 A 19961217
WO 1997-US15179 W 19970828

AB The present invention provides nucleic acid and corresponding amino acid sequences of a multifunctional enzyme that has been found to be useful in numerous medical and cosmetic contexts. The krill-derived enzyme isoforms are multifunctional proteinases having at least one of the following: chymotrypsin, trypsin, collagenase, **elastase**, exopeptidase, or asialo GM1 ceramide-binding activities. These enzymes can be used to treat viral infections, blood clots, wounds, immune disorders including autoimmune diseases, such as lupus erythematosus and **multiple sclerosis**, and cancer. Other uses for these enzymes include digesting proteinaceous material for purposes such as cleaning and creating improved feeds for animals or bacteriol. Expression vectors contg. genes encoding these enzymes can be cloned in host eukaryotic or prokaryotic host organisms, and pharmaceutical compns. prepd. from the isolated and purified enzymes.

IT **9004-06-2, Elastase**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cloning, sequence, and expression of multifunctional enzyme isoform genes from krill)

L7 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:110513 CAPLUS
DOCUMENT NUMBER: 110:110513
TITLE: Enzyme immunoassay of **medullasin** in peripheral blood
AUTHOR(S): Aoki, Yosuke; Yoshida, Mitsuo; Kominami, Eiki
CORPORATE SOURCE: Dep. Biochem. Nutr., Inst. Public Health, Tokyo, Japan
SOURCE: Clin. Chim. Acta (1988), 178(2), 193-204
CODEN: CCATAR; ISSN: 0009-8981
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An enzyme immunoassay method for the detn. of the amt. of **medullasin**, a serine protease in granulocytes, was developed. Beads coated with IgG obtained from immunized rabbits were incubated with **medullasin**, Fab'-peroxidase conjugate was added, and peroxidase activity bound to beads was measured by a fluorophotometer. The amt. of **medullasin** detd. by this method correlated well with the value calcd. from the protease activity measured by the conventional method. The min. detectable amt. of **medullasin** was 300 pg. Granulocytes obtained from patients with **multiple sclerosis** in active phase and those from patients with Behcet's disease in relapse showed elevated levels of **medullasin** as compared with normal controls. However, the amt. of **medullasin** in granulocytes

obtained from patients in remission revealed normal values. These results indicate that elevated levels of **medullasin** activity in granulocytes of these diseases in relapse is due to an increased amt. of **medullasin** in granulocytes and that the normalization of **medullasin** activity in remission is the result of the decrease of the amt. of **medullasin** in granulocytes.

IT **83682-98-8, Medullasin**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in granulocyte of human in health and **multiple sclerosis** and Behcet's syndrome)

L7 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:31374 CAPLUS
DOCUMENT NUMBER: 100:31374
TITLE: Differential isoelectric focusing properties of crude and purified human .alpha.2-macroglobulin and .alpha.2-macroglobulin-proteinase complexes
AUTHOR(S): Back, Stephen A.; Alhadeff, Jack A.
CORPORATE SOURCE: Dep. Neurosci., Univ. California, San Diego, La Jolla, CA, 92093, USA
SOURCE: J. Chromatogr. (1983), 278(1), 43-51
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The column isoelec. focusing (IEF) properties of human .alpha.2-macroglobulins (.alpha.2M) and .alpha.2M-proteinase complexes from crude and partially purified prepns. were studied. The av. isoelec. point (pI) of the major form was 6.5 for .alpha.2M from crude plasma but was 5.3 for purified samples. Following preincubation with either trypsin, chymotrypsin, or pancreatic **elastase**, the crude .alpha.2M-proteinase complexes displayed pI values ranging 5.3-6.1 and the purified .alpha.2M-proteinase complexs ranged pH 6.0-6.1. A comparison of recoveries for focused crude or purified .alpha.2M and trypsin-preincubated .alpha.2M indicated enhanced recovery for the trypsin-preincubated samples, suggesting that the binding of the proteinase enhances the stability of .alpha.2M. .alpha.2M thus displays column IEF properties which appear to be dependent upon the state of purity of the mol. These findings are of particular significance to investigators concerned with using expressions of altered .alpha.2M electrophoretic patterns for clin. diagnostic purposes in such diseases as **multiple sclerosis**, diabetes, and cystic fibrosis.

IT **9004-06-2D**, .alpha.2-macroglobulin complexes
RL: PROC (Process)
(isoelec. focusing of, purity in relation to)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,

JICST-EPLUS, JAPIO' ENTERED AT 14:39:25 ON 23 APR 2001)
L8 30 S L7
L9 21 DUP REM L8 (9 DUPLICATES REMOVED)

L9 ANSWER 1 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-594139 [56] WPIDS
CROSS REFERENCE: 2000-572151 [50]; 2000-587294 [50]; 2000-611339 [50]
DOC. NO. CPI: C2000-177373
TITLE: Treating excessive apoptosis, e.g. cancer or neurodegeneration, by administering inhibitor of serine protease, e.g. alpha1-antitrypsin or analog.
DERWENT CLASS: B02 B03
INVENTOR(S): SHAPIRO, L
PATENT ASSIGNEE(S): (UYTE-N) UNIV TECHNOLOGY CORP
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000051624	A2	20000908	(200056)*	EN	29
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2000037314	A	20000921	(200065)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000051624	A2	WO 2000-US6069	20000303
AU 2000037314	A	AU 2000-37314	20000303

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000037314	A Based on	WO 200051624

PRIORITY APPLN. INFO: US 1999-123167 19990305
AN 2000-594139 [56] WPIDS
CR 2000-572151 [50]; 2000-587294 [50]; 2000-611339 [50]
AB WO 200051624 A UPAB: 20001214
NOVELTY - Treatment of diseases associated with excessive apoptosis comprises administering at least one inhibitor (I) of serine

protease (SP).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) prophylactic treatment of subjects at risk of developing an apoptotic disease by administering at least one agent (Ia) with mammalian alpha 1-antitrypsin (aaT) or aaT-like activity;

(2) inhibiting apoptosis in vitro in mammalian cells, ex vivo in mammalian tissue cultures and organs by administering (I);

(3) inhibiting apoptosis by treating cells with (I); and

(4) sustaining aaT activity in blood by administering (i) aaT to replace inactivated aaT or (ii) a variant of aaT, or a synthetic aaT, that is not inactivated by free radicals.

ACTIVITY - Cytostatic; immunosuppressive; antiarthritic; antiinflammatory; antidiabetic; neuroprotective; antibacterial; vasotropic; hepatotropic; anti-HIV; cerebroprotective.

MECHANISM OF ACTION - Serine protease inhibitor; oxygen free radical inhibitor; oxygen free radical formation inhibitor.

Rat brain cerebral granule cells were incubated for 10 hours in (i) conditioned medium with serum; (ii) Eagle basic medium (EBM) without serum or (iii) EBM containing 60 micro M of the peptoid (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I'). The cells were then fixed, stained and analyzed for apoptosis. The proportion of apoptotic cells was less than 5% in (i), about 45% in (ii) and about 8% in (iii).

USE - The method is used to treat or prevent cancer; autoimmune diseases (e.g. arthritis, **multiple sclerosis** or diabetes); neurodegeneration; sepsis; ischemic reperfusion injury; toxin-mediated liver disease; acquired immune deficiency syndrome (AIDS), or particularly myocardial infarction and stroke. (I) may also be used to inhibit apoptosis in vivo or ex vivo, e.g. in cell cultures, tissues and organs and to sustain endogenous levels of aaT.

ADVANTAGE - The treatment is effective against apoptosis however this is induced in a wide range of organs.

Dwg.0/2

L9 ANSWER 2 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER:	2000-572151 [53] WPIDS
CROSS REFERENCE:	2000-587294 [50]; 2000-594139 [50]; 2000-611339 [50]
DOC. NO. CPI:	C2000-170609
TITLE:	Treating disease e.g. autoimmune disease and hypertension by administering agent which inhibits nitric oxide synthesis and e.g. alpha1-antitrypsin.
DERWENT CLASS:	B05 C03 D16
INVENTOR(S):	SHAPIRO, L
PATENT ASSIGNEE(S):	(UYTE-N) UNIV TECHNOLOGY CORP
COUNTRY COUNT:	87

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000051623	A2	20000908	(200053)*	EN	49

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000035115 A 20000921 (200065)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000051623	A2	WO 2000-US5556	20000303
AU 2000035115	A	AU 2000-35115	20000303

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000035115	A	Based on	WO 200051623

PRIORITY APPLN. INFO: US 1999-156523 19990929; US 1999-123167 19990305

AN 2000-572151 [53] WPIDS

CR 2000-587294 [50]; 2000-594139 [50]; 2000-611339 [50]

AB WO 200051623 A UPAB: 20001214

NOVELTY - Diseases are treated by administering at least one agent (I) that:

(1) suppresses nitric oxide (NO) synthesis and

(2) has mammalian alpha 1-antitrypsin (aaT), aaT-like, **elastase**-inhibiting or proteinase-3-inhibiting activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(I) treating subjects at risk of diseases produced, at least partly, by inappropriate NO, by administering at least one agent with aaT, aaT-like, **elastase**-inhibiting or proteinase-3-inhibiting activity;

(II) inhibiting NO production in cells by treatment with at least one agent having aaT, aaT-like or serine protease inhibiting activity;

(III) a composition comprising at least one agent having aaT or aaT-like activity and a free radical scavenger or antioxidant;

(IV) treating ischemic reperfusion injury by administering at

least one of aaT, aaT-like agent, antielastase or antiproteinase-3 agent or serine protease (SP) inhibitor;

(V) sparing tissue levels of aaT by administering an inhibitor of NO synthase and

(VI) treating disease associated with high levels of NO synthesis by administering at least one inhibitor of a proteinase-activated receptor.

ACTIVITY - Antiinflammatory; neuroprotective; immunostimulant; antiasthmatic; antiarteriosclerotic; immunosuppressant; cytostatic; Cerebroprotective; hepatotropic; ophthalmological; cardiant; antimalarial; gastrointestinal; analgesic; hypotensive; antiarthritic; antidiabetic; antihypertensive; antitumor; protozoacide; antiviral; respiratory; antianemic; dermatological.

MECHANISM OF ACTION - Nitric oxide synthesis inhibitor; serine protease inhibitor; trypsin inhibitor; **elastase** inhibitor; proteinase-3 inhibitor.

(Benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (I') was tested for inhibition of NO synthesis, produced by inducible NO synthase after induction with 0.5 ng/ml lipopolysaccharide and 10 units/ml of interferon- gamma , in RAW264.5 macrophages. In absence of (Ia), synthesis was 90 nmole per million cells, but in the presence of 60 mu M (Ia) it was only 10 nmole per million cells.

USE - Used in human or veterinary medicine for treating tubulointerstitial disease, acute pancreatitis, acute respiratory failure or distress syndrome, age associated memory impairment, AIDS, airway inflammation, Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, autoimmune myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular accident, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic otitis media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end stage renal disease, falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, hot dog headache, Hirschsprung's disease, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease, inflammatory joint diseases, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, **multiple sclerosis**, myocardial infarction, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus

erythematosus, traumatic brain injury, tumor progression and vascular disease.

ADVANTAGE - Treatment with (I) reduces NO-mediated side effects associated with treating cancer with interleukin-2 or tumor necrosis factor and prevents inactivation of endogenous aaT by peroxynitrite (derived from NO).

Dwg.0/7

L9 ANSWER 3 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-465949 [40] WPIDS
DOC. NO. CPI: C2000-140344
TITLE: New amide derivatives, useful for treatment of emphysema, neoplasia, atherosclerosis, chronic inflammatory conditions, arthritis, corneal ulceration, and neurological disorders, are selective **matrix metalloproteinase 12** inhibitors.
DERWENT CLASS: B05
INVENTOR(S): JANUSZ, M J; WARSHAWSKY, A M
PATENT ASSIGNEE(S): (AVET) AVENTIS PHARM INC
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000040600	A1	20000713	(200040)*	EN	80
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2000017197	A	20000724	(200052)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000040600	A1	WO 1999-US26749	19991112
AU 2000017197	A	AU 2000-17197	19991112

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000017197	A Based on	WO 200040600

PRIORITY APPLN. INFO: US 1998-224550 19981231

AN 2000-465949 [40] WPIDS
AB WO 200040600 A UPAB: 20000823
NOVELTY - Sulfur containing polyamides (I) are new.
DETAILED DESCRIPTION - Sulfur containing polyamides of formula (I), salts, stereoisomers and hydrates are new.
R1 = H, 1-6C alkyl, (CH2)aCO2R5, (CH2)aC(O)NH2, (CH2)4NH2, (CH2)3NHC(NH)NH2, (CH2)2S(O)bCH3, CH2OH, CH(OH)CH3, CH2SH, (CH2)dAr1 or CH2Ar2;
R2 = 1-6C alkyl, (CH2)eCO2R5, (CH2)eC(O)NH2, (CH2)4NH2, (CH2)3NHC(NH)NH2, (CH2)2S(O)fCH3, CH2OH, CH(OH)CH3, CH2SH, (CH2)gAr1 or CH2Ar2;
R3 = 1-6C alkyl, (CH2)mW', (CH2)pAr3, (CH2)kCO2R9, (CH2)mSO2N(R8')Y1, (CH2)mZ'Q;
a, e = 1 - 2;
b, f = 0 - 2;
d = 0 - 4;
g = 1 - 4;
R5 = H, 1-4C alkyl or benzyl;
Ar1 = phenyl substituted by 1 - 2 R6 or naphthyl substituted by R7;
R6 = H, halogen, 1-4C alkyl, OH or 1-4C alkoxy;
R7 = H, halogen, 1-4C alkyl or 1-4C alkoxy;
Ar2 = indol-3-yl or imidazol-4-yl;
m = 2 - 8;
p = 0 - 10;
k = 1 - 9;
W' = phthalimido;
Ar3 = phenyl (substituted by 1 - 2 R23), quinolinyl, imidazolyl, thienyl, furanyl or pyridyl;
R23 = H, halogen, 1-4C alkyl or 1-4C alkoxy;
R8', R9 = H or 1-6C alkyl;
Y1 = H, (CH2)jAr4, N(R24)2; or
NY1R8' = N-morpholino, N-piperidino, N-pyrrolidino or N-isoindolyl;
j = 0 - 1;
R24 = H or 1-6C alkyl;
Ar4 = phenyl substituted by 1 - 3 R25;
R25 = H, halogen, 1-4C alkyl or 1-4C alkoxy;
Z' = O, NR8, C(O)NR8, N(R8)C(O), N(R8)C(O)NH, N(R8)C(O)O or OC(O)NH;
R8 = H or 1-6C alkyl;
Q = H, (CH2)nY2 or (CH2)xY3;
n = 0 - 4;
Y2 = H, (CH2)hAr5 or (CH2)tC(O)OR27;
Ar5 = phenyl (substituted by 1 - 3 R26) or quinolinyl;
R26 = H, halogen, 1-4C alkyl or 1-4C alkoxy;
h = 0 - 6;
t = 1 - 6;

R27 = H or 1-6C alkyl;
x = 2 - 4;
Y3 = N(R28)2, N-morpholino, N-piperidino, N-pyrrolidino or N-isoindolyl;
R28 = H or 1-6C alkyl;
R4 = H, C(O)R10, C(O)(CH2)qX or S-G;
R10 = H, 1-4C alkyl, phenyl or benzyl;
q = 0 - 2;
X = pyridinyl, imidazol-1-yl, NR11R11', phenyl substituted by NR11R11', or a group of formula (i);
V' = CH2, O, S(O)r, NR21 or NC(O)R22;
r = 0 - 2;
R21 = H, 1-4C alkyl or benzyl;
R22 = H, CF3, 1-10C alkyl, phenyl or benzyl;
R11, R11' = H, 1-4C alkyl or benzyl;
G = pyrid-2-yl, (CH2)w-phenyl (substituted by 1 - 2 R14) or a group of formula (ii) - (vi);
w = 1 - 3;
R12 = H, 1-6C alkyl, CH2CH2S(O)uCH3 or benzyl;
u = 0 - 2;
R13 = H, OH, amino, 1-6C alkyl, N-methylamino, N,N-dimethylamino, CO2R17 or OC(O)R18;
R17 = H, CH2OC(O)C(CH3)3, 1-4C alkyl, benzyl or diphenylmethyl;
R18 = H, 1-6C alkyl or phenyl;
R14 = H, 1-4C alkyl, 1-4C alkoxy or halogen;
V1 = O, S or NH;
V2 = N or CH;
V3 = bond or C(O);
V4 = O, S, NR19 or NC(O)R20;
R19 = H, 1-4C alkyl or benzyl;
R20 = H, CF3, 1-10C alkyl or benzyl;
R15 = H, 1-6C alkyl or benzyl; and
R16 = H or 1-4C alkyl.

ACTIVITY - Respiratory (claimed); cytostatic; antiarteriosclerotic; antiinflammatory; antiasthmatic; antirheumatic; Antiarthritic; osteopathic; ophthalmological; antibacterial; neuroprotective.

MECHANISM OF ACTION - Matrix metalloproteinase 12 (MMP 12) inhibitor.

(I) were incubated with MMP-12 and the fluorogenic substrate Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH2 (Mca, Dpa not defined) in assay buffer, with reaction followed at 405 nm. 2-Mercaptopentanoyl-L-homophenylalanyl-L-phenylalanine (Ia) had a Ki of 13 nM, compared with 5800 nM for MMP-1, 1800 nM for MMP-2 and 750 nM for MMP-3.

USE - As a matrix metalloproteinase inhibitor for treatment of smoking induced emphysema (claimed). Also for treatment of neoplastic states (e.g. leukemias, carcinomas, adenocarcinomas, sarcomas, melanomas and mixed neoplasias), atherosclerosis, chronic

inflammatory conditions such as chronic bronchitis and asthma, rheumatoid arthritis, osteoarthritis, corneal ulceration, dental diseases such as gingivitis and periodontitis and neurological disorders such as multiple sclerosis.

ADVANTAGE - Selective for matrix metalloproteinase 12.

Dwg.0/0

L9 ANSWER 4 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-465936 [40] WPIDS
DOC. NO. CPI: C2000-140331
TITLE: New benzazepine derivatives, useful for treatment of neoplastic states, atherosclerosis and inflammatory diseases such as emphysema, chronic bronchitis and asthma, are matrix metalloproteinase inhibitors .
DERWENT CLASS: B02 C02
INVENTOR(S): FLYNN, G A; JANUSZ, M J; WARSHAWSKY, A
PATENT ASSIGNEE(S): (AVET) AVENTIS PHARM INC
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000040564	A1	20000713	(200040)*	EN	108
AU 2000018369	A	20000724	(200052)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000040564	A1	WO 1999-US28339	19991130
AU 2000018369	A	AU 2000-18369	19991130

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000018369	A Based on	WO 200040564

PRIORITY APPLN. INFO: US 1998-224549 19981231
AN 2000-465936 [40] WPIDS
AB WO 200040564 A UPAB: 20000823

Searcher : Shears 308-4994

NOVELTY - Benzolactam derivatives (I) are new.

DETAILED DESCRIPTION - Benzolactam derivatives of formula (I), salts, stereoisomers and hydrates, are new.

A = OH or NRR';

R, R' = H or 1-6C alkyl; or

NRR' = N-morpholino, N-piperidino, N-pyrrolidino or N-isoindolyl;

R1 = H, 1-6C alkyl, (CH2)aCO2R5, (CH2)aC(O)NH2, (CH2)4NH2, (CH2)3NHC(NH)NH2, (CH2)2S(O)bCH3, CH2OH, CH(OH)CH3, CH2SH, (CH2)dAr1 or CH2Ar2;

a = 1 - 2;

b = 0 - 2;

d = 0 - 4;

R5 = H, 1-4C alkyl or benzyl;

Ar1 = phenyl substituted by 1 - 2 R6 or naphthyl substituted by R7;

R6 = H, halogen, 1-4C alkyl, OH or 1-4C alkoxy;

R7 = H, halogen, 1-4C alkyl or 1-4C alkoxy;

Ar2 = indol-3-yl or imidazol-4-yl;

R2 = H, halogen, OH, 1-4C alkyl or 1-4C alkoxy;

R3 = 1-6C alkyl, (CH2)mW', (CH2)pAr3, (CH2)kCO2R9, (CH2)mN(R8)SO2Y1 or (CH2)mZ'Q;

m = 2 - 8;

p = 0 - 10;

k = 1 - 9;

W' = phthalimido;

Ar3 = phenyl (substituted by 1 - 2 R23), quinolinyl, imidazolyl, thienyl, furanyl or pyridyl;

R23 = H, halogen, 1-4C alkyl or 1-4C alkoxy;

R8, R9 = H or 1-6C alkyl;

Y1 = H, (CH2)jAr4 or N(R24)2;

j = 0 - 1;

R24 = H or 1-6C alkyl; or

NR24R24 = N-morpholino, N-piperidino, N-pyrrolidino or N-isoindolyl;

Ar4 = phenyl substituted by 1 - 3 R25;

R25 = H, halogen, 1-4C alkyl or 1-4C alkoxy;

Z' = O, NR8, C(O)NR8, N(R8)C(O), N(R8)C(O)NH, N(R8)C(O)O or OC(O)NH;

R8 = H or 1-6C alkyl;

Q = H, (CH2)nY2 or (CH2)xY3;

n = 0 - 4;

Y2 = H, (CH2)hAr5 or (CH2)tC(O)OR27;

Ar5 = phenyl (substituted by 1 - 3 R26) or quinolinyl;

R26 = H, halogen, 1-4C alkyl or 1-4C alkoxy;

h = 0 - 6;

t = 1 - 6

R27 = H or 1-6C alkyl;

x = 2 - 4;
Y3 = N(R28)2, N-morpholino, N-piperidino, N-pyrrolidino or N-isoindolyl;
R28 = H or 1-6C alkyl;
R4 = H, C(O)R10, C(O)(CH2)qK' or SG;
q = 0 - 2;
K = pyridyl, imidazol-1-yl, NR11R11, phenyl substituted by NR11R11 or a group of formula (i);
V' = bond, CH2, O, S(O)r, NR21 or NC(O)R22;
r = 0 - 2;
R11, R21 = H, 1-4C alkyl or benzyl;
R22 = H, CF3, 1-10C alkyl, phenyl or benzyl;
G = pyrid-2-yl, (CH2)w-pyridyl, (CH2)w-phenyl substituted by 1 - 2 R14, or a group of formula (ii) - (v);
w = 1 - 3;
R12 = H, 1-6C alkyl, CH2CH2S(O)uCH3 or benzyl;
u = 0 - 2;
R13 = H, OH, amino, 1-6C alkyl, N-methylamino, N,N-dimethylamino, CO2R17 or OC(O)R18;
R17 = H, CH2OC(O)C(CH3)3, 1-4C alkyl, benzyl or diphenylmethyl;
R18 = H, 1-6C alkyl or phenyl;
R14 = H, 1-4C alkyl, 1-4C alkoxy or halogen;
V1 = O, S or NH;
V2 = N or CH;
V3 = bond or C(O);
V4 = O, S, NR19 or NC(O)R20 (sic);
R19 = H, 1-4C alkyl or benzyl;
R20 = H, CF3, 1-10C alkyl or benzyl;
R15 = H, 1-6C alkyl or benzyl; and
R16 = H or 1-4C alkyl.

ACTIVITY - Cytostatic; antiarteriosclerotic; antiinflammatory; respiratory; antiasthmatic; antirheumatic; antiarthritic; osteopathic; cardiovascular; ophthalmological; antibacterial; neuroprotective.

MECHANISM OF ACTION - Matrix metalloproteinase 12 inhibitor (claimed).

No biological data given.

USE - As a matrix metalloproteinase inhibitor (claimed) for treatment of neoplastic states (claimed) such as leukemias, carcinomas, adenocarcinomas, sarcomas, melanomas and mixed neoplasias, atherosclerosis (claimed), chronic inflammatory disease (claimed) such as emphysema, chronic bronchitis and asthma, rheumatoid arthritis, osteoarthritis, cardiovascular disorders, corneal ulceration, dental diseases (e.g. gingivitis and periodontitis) and neurological disorders such as multiple sclerosis.

ADVANTAGE - Selective for matrix metalloproteinase 12 (MMP-12).

Dwg.0/0

L9 ANSWER 5 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-256367 [22] WPIDS
DOC. NO. CPI: C2000-078168
TITLE: Synthetic antiinflammatory peptide derived from IL-2 and its derivatives useful for treating inflammatory autoimmune diseases such as rheumatoid arthritis, **multiple sclerosis** and systemic lupus erythematosus.
DERWENT CLASS: B04 D16
INVENTOR(S): ARIEL, A; FRIDKIN, M; HERSHKOVIZ, R; LIDER, O; YAVIN, E J
PATENT ASSIGNEE(S): (YEDA) YEDA RES & DEV CO LTD
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000011028	A2	20000302	(200022)*	EN	49
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9953002	A	20000314	(200031)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000011028	A2	WO 1999-IL448	19990819
AU 9953002	A	AU 1999-53002	19990819

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9953002	A	Based on	WO 200011028

PRIORITY APPLN. INFO: IL 1999-129980 19990516; GB 1998-18370 19980821; IL 1998-126009 19980831
AN 2000-256367 [22] WPIDS
AB WO 200011028 A UPAB: 20000508
NOVELTY - A synthetic antiinflammatory peptide (I) derived from IL-2 and its antiinflammatory derivatives, is new.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for selecting (I), comprising:

(a) digesting IL-2 with a proteolytic enzyme that participates in the breakdown of extra cellular matrix (ECM);

(b) testing the fractions obtained in (a) for their in vitro ability to inhibit adhesion and chemotactic migration of activated T-cells to ECM proteins, cytokine or mitogen induced T-cell proliferation and spontaneous or induced cytokine secretion;

(c) selecting the fractions to identify individual peptides and submitting each identified peptide to sequencing and analysis; and

(d) carrying out one or more of the bioassays of (b) with the identified synthetic peptides that show significant inhibitory activity.

ACTIVITY - Antiinflammatory; antiarthritic; antirheumatic; antidiabetic; neuroprotective; dermatological; immunosuppressive; opthalmological.

MECHANISM OF ACTION - Inhibitor of adhesion of activated T-cells to ECM proteins such as fibronectin (FN), laminin (LN), collagen type-IV (CO-IV); inhibitor of chemotactic migration of T-cell through ECM proteins preferably FN; inhibitor of cytokine or mitogen induced T-cell proliferation; inhibitor of spontaneous or induced, preferably TNF- alpha induced cytokine secretion (e.g.IL-8, IL-1 beta) by stimulated T-cells and intestinal epithelial cells (claimed).

The effect of three IL-2 derived peptides (pep1, pep2, pep3) on the interaction of T-cells with ECM glycoproteins (FN), (LN), (CO-IV) was determined by exposing 10 pg/ml of the three peptides to T-cells and activating with IL-2. The treated cells were then added to microtiter wells coated with (FN), (LN) (CO-IV). The result indicated that all the three peptides inhibited T-cell adhesion to all the three major cell adhesive glycoproteins of ECM.

USE - (I) is useful for preparing compositions for treating and/or alleviating chronic or acute inflammatory disorders and autoimmune diseases such as rheumatoid arthritis, diabetes type-I, **multiple sclerosis**, systemic lupus erythematosus, uveitis, bowel inflammation and Crohn's disease (claimed).

Dwg.0/8

L9 ANSWER 6 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-401197 [35] WPIDS

DOC. NO. CPI: C2000-121555

TITLE: Use of new or known N-heterocyclyl 4-phenyl-2-hydroxybutylamine or 4-phenyl-2-hydroxybutyramide derivatives to prepare antiinflammatory medicaments.

DERWENT CLASS: B02

INVENTOR(S): EKERDT, R; GIESEN, C; KALKBRENNER, F; KROLIKIEWICZ, K; LEHMANN, M; SKUBALLA, W; STREHLKE, P

PATENT ASSIGNEE(S): (SCHD) SCHERING AG

COUNTRY COUNT: 90

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 19856475	A1	20000531	(200035)*		28
WO 2000032584	A2	20000608	(200035)	GE	

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000019760 A 20000619 (200044)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19856475	A1	DE 1998-19856475	19981127
WO 2000032584	A2	WO 1999-EP9754	19991129
AU 2000019760	A	AU 2000-19760	19991129

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000019760	A	Based on	WO 200032584

PRIORITY APPLN. INFO: DE 1998-19856475 19981127

AN 2000-401197 [35] WPIDS

AB DE 19856475 A UPAB: 20000725

NOVELTY - Use of N-heterocyclyl 4-phenyl-2-hydroxybutylamine or 4-phenyl-2-hydroxybutyramide derivatives (I) to prepare medicaments with antiinflammatory activity is claimed.

DETAILED DESCRIPTION - The use of compounds of formula (I) to prepare medicaments with antiinflammatory activity is claimed:

R1, R2 = H or 1-5C alkyl or are linked to form a 3- to 7-membered ring;

R3 = 1-5C alkyl or 1-5C (per)fluoroalkyl;

A = a group of formula (i):

R4 = H, 1-5C alkyl, 1-10C acyl, 3-10C alkoxycarbonylalkyl, 2-5C cyanoalkyl, 3-10C optionally substituted allyl, 3-10C optionally substituted propargyl, 2-5C alkoxyalkyl or 1-5C (per)fluoroalkyl;

R5-R8 = H, halogen or 1-5C alkoxy;

B = CO or CH2;

Ar = a group of formula (ii)-(v):

X3, X3', Y4 = H, 1-5C alkyl or 1-5C (per)fluoroalkyl;

X4, X6, X7, Y5, Y7, Y8 = H, 1-5C alkyl, 1-5C (per)fluoroalkyl, halogen, OH, 1-5C alkoxy or 1-5C alkanoyloxy;

alternatively, R4 and R5 are linked to form a 5- to 7-membered ring optionally containing other heteroatom(s) selected from O, N and S.

An INDEPENDENT CLAIM is also included for the following compounds (I):

5 -(3-(1-(5-fluoro-2-methoxyphenyl)-cyclopropyl)-2-hydroxy-2-trifluoromethyl-propionylamino)-phthalide;

5-(3-(1-(5-fluoro-2-hydroxyphenyl)-cyclopropyl)-2-hydroxy-2-trifluoromethyl-propionylamino)-phthalide;

4-bromo-5-(4-(5-fluoro-2 -hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentylamino)-phthalide;

4-bromo-5-(4 -(3-bromo-5-fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentylamino)-phthalide;

6-(3-(1-(5-fluoro-2-hydroxyphenyl)-cyclopropyl)-2-hydroxy-2-trifluoromethyl-propionylamino)-4-methyl-2,3-benzoxazin-1-one;

6-(2-hydroxy-4-(2-hydroxyphenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-4-ethyl-2,3-benzoxazin-1-one;

6-(4-(4-bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentylamino)-4-methyl-2,3-benzoxazin-1-one;

5-(3-(1-(5-fluoro-2-methoxyphenyl)-cyclopropyl)-2-hydroxy-2-trifluoromethyl-propionylamino)-phthalide;

6-(2-hydroxy-4-(5-fluoro -2-methoxyphenyl)-4-methyl-2-trifluoromethyl-pentylamino)-4-methyl-2,3-benzoxazin-1-one;

5-(3-(1-(5-fluoro-2-hydroxyphenyl)-cyclopropyl)-2-hydroxy-2-trifluoromethyl-propionylamino)-phthalide;

6-(3-(1-(5-fluoro-2-hydroxyphenyl)-cyclopropyl)-2-hydroxy-2-trifluoromethyl-propionylamino)-4-methyl-2,3-benzoxazin-1-one;

(-)-4-bromo-5-(4-(5-fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentylamino)-phthalide;

(-)-4-bromo-5-(4-(3-bromo-5-fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentylamino)-phthalide;

5-(2-hydroxy-4-(5-isopropyl-2-methoxyphenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-phthalide;

5-(2-hydroxy-4-(2-methoxy-5-propylphenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-phthalide;

5-(2-hydroxy-4-(2-benzyloxy-5-fluorophenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-phthalide;

5-(2-hydroxy-4-(2-difluoromethoxy-5-fluorophenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-phthalide;

5-(2-hydroxy-4-(5-fluoro-2-methoxymethoxyphenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-phthalide;

5-(2-hydroxy-4-(2-ethoxymethoxy-5-fluorophenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-phthalide;

5-(2-hydroxy-4-(5-fluoro-2-(2-methoxyethoxy)-phenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-phthalide.

ACTIVITY - Antiinflammatory; antiallergic; immunosuppressant;

antiproliferative.

Topical and system administration of unspecified compounds (I) inhibited 3 parameters of inflammation induced by topical application of croton oil to the ears of rats and mice, i.e. edema, peroxidase activity and elastase activity (no data given).

MECHANISM OF ACTION - Glucocorticoid receptor (GR) ligand; cytokine secretion inhibitor.

5-(2-Hydroxy-4-(5-fluoro-2-hydroxymethoxyphenyl)-4-methyl-2-trifluoromethyl-valeroylamino)-phthalide had an IC50 of 2.8 nM against binding of (3H)-dexamethasone to a rat thymus homogenate cytosol preparation, compared with 20 nM for dexamethasone.

Unspecified compounds (I) inhibited secretion of interleukin-8 and tumor necrosis factor alpha by THP-1 human monocytes stimulated with phorbol ester and ionomycin (no data given).

USE - (I) are non-steroidal antiinflammatory agents which also have antiallergic, immunosuppressant and antiproliferative activity and are useful for treating lung diseases (e.g. asthma, bronchitis), rheumatic and autoimmune diseases (e.g. rheumatoid arthritis, polymyositis), allergies, dermatological disorders (e.g. psoriasis, rosacea), liver, kidney, gastrointestinal and proctological diseases (e.g. fissures, hemorrhoids), eye diseases (e.g. conjunctivitis), ear, nose and throat diseases (e.g. allergic rhinitis, otitis media), neurological diseases (e.g. multiple sclerosis, encephalomyelitis), blood diseases (e.g. idiopathic cytopenia), tumors (e.g. acute lymphatic leukemia, lymphosarcoma), endocrine disorders, transplant rejection, severe shock, renal insufficiency and emesis (no data given).

ADVANTAGE - (I) show a clear dissociation between antiinflammatory activity and metabolic (especially hepatic) side effects. Unspecified compounds (I) caused little or no induction of tyrosine aminotransferase activity in rat liver (no data given).

Dwg.0/0

L9 ANSWER 7 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 2001:39753 BIOSIS

DOCUMENT NUMBER: PREV200100039753

TITLE: MMS in human cerebral endothelial cells: Shedding of adhesion molecules.

AUTHOR(S): Hummel, V. (1); Kallmann, B. (1); Fueller, T.; Wagner, S.; Tonn, J.; Benveniste, E.; Rieckmann, P. (1)

CORPORATE SOURCE: (1) Clinical Research Unit for MS, Dept. of Neurology, Julius-Maximilians-Universitaet, D-97080, Wuerzburg Germany

SOURCE: FASEB Journal, (April 20, 2000) Vol. 14, No. 6, pp. A1152. print.
Meeting Info.: Joint Annual Meeting of the American Association of Immunologists and the Clinical

Immunology Society Seattle, Washington, USA May 12-16, 2000
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L9 ANSWER 8 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 2000:482865 BIOSIS
DOCUMENT NUMBER: PREV200000482865
TITLE: Determination of **medullasin** levels for the diagnosis of **multiple sclerosis**.
AUTHOR(S): Aoki, Y. (1); Saida, T.; Nakano, I.; Saito, T.; Ikeguchi, K.; Urabe, T.; Nishiguchi, E.; Suzuki, H.; Takahashi, K.; Katsuragi, H.; Mizuno, Y.
CORPORATE SOURCE: (1) Department of Food and Health Sciences, Faculty of Human Life Sciences, Jisssen Women's University, Osakaue 4-1-1, Hino-City, Tokyo, 191-8510 Japan
SOURCE: Acta Neurologica Scandinavica, (October, 2000) Vol. 102, No. 4, pp. 218-221. print.
ISSN: 0001-6314.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objectives: To obtain a simple and reliable clinical parameter for the diagnosis of **multiple sclerosis** among patients with neurological diseases. Patients and methods: Heparinized peripheral blood was obtained from patients with **multiple sclerosis** and those with non-inflammatory neurological diseases and healthy volunteers. A new enzyme immunoassay method determining **medullasin** levels in human granulocytes was developed by using mouse monoclonal antibody against **medullasin**. Results: A newly developed enzyme immunoassay method for **medullasin** can detect as little as 1 ng/ml **medullasin** and results can be obtained within 2 h. Eighty-five out of 112 patients with **multiple sclerosis** (75.8%) showed positive results (above means of normals+2 SD) in the **medullasin** test, while 15.4% (12/78) of patients with non-inflammatory neurological disease had positive results. Conclusion: This newly developed enzyme immunoassay method for **medullasin** is considered to be a useful paraclinical test for the diagnosis of **multiple sclerosis**.

L9 ANSWER 9 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000164376 EMBASE
TITLE: First anniversary editorial.
AUTHOR: Hagmann W.K.; McMillan R.
CORPORATE SOURCE: W.K. Hagmann, Merck Research Laboratories, PO Box

2000, Rahway, NJ 07065-0900, United States
SOURCE: Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs, (2000) 2/2 (i-ii).
ISSN: 1464-8474 CODEN: COAIFF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 037 Drug Literature Index
015 Chest Diseases, Thoracic Surgery and Tuberculosis
008 Neurology and Neurosurgery
031 Arthritis and Rheumatism
LANGUAGE: English

L9 ANSWER 10 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-347260 [29] WPIDS
DOC. NO. CPI: C1999-102154
TITLE: New carbocyclic and heterocyclic ring-containing compound tryptase inhibitors, used for treating e.g. inflammatory or allergic disease, especially asthma.
DERWENT CLASS: B05 B07
INVENTOR(S): BURGESS, L; RIZZI, J P; BURGESS, L E
PATENT ASSIGNEE(S): (ARRA-N) ARRAY BIOPHARMA INC; (AMGE-N) AMGEN INC
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9924395	A1	19990520	(199929)*	EN	144
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
AU 9913012	A	19990531	(199941)		
ZA 9810046	A	20000126	(200011)		142

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9924395	A1	WO 1998-US23361	19981103
AU 9913012	A	AU 1999-13012	19981103
ZA 9810046	A	ZA 1998-10046	19981103

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9913012	A	Based on	WO 9924395

PRIORITY APPLN. INFO: US 1998-179781 19981027; US 1997-65026 19971110

AN 1999-347260 [29] WPIDS

AB WO 9924395 A UPAB: 19990723

NOVELTY - Compounds (I) containing at least 4 carbocyclic and/or heterocyclic rings are new.

DETAILED DESCRIPTION - Carbocyclic and heterocyclic ring-containing compounds of formula (I) and their salts, esters and solvates are new.

Ar, Ar' = aryl, heteroaryl or 5-7 membered carbocyclic or heterocyclic ring;

A = -((CH2)m-CO)r-NR2-(CH2)m- or -((CH2)m-CO)r-NR2-CH(COOH)-;

B' = -((D)r-(CH2)m) or (CH2)m, provided that if B' = ((D)r-(CH2)m), then m is not 0;

D = O, S, SO2, CO or NH;

X = CO, (CH2)m or SO2;

Y = R1NH-C(=NH)-, R1NH-CONH-, N triple bond C- or R1NH-(CH2)v-, CH3SO2NH(CH2)v, OH, SH, CF3, F, Cl, Br, I, H, 1-4C alkoxy, aryl, heteroaryl, 1-4C acyloxy, 1-4C alkyl, 1-4C alkylthio or NO2;

Z' = (CH2)m, O, S, SO2, NH, (CH2)v-C=C-(CH2)v (sic), (CH2)v-C triple bond C-(CH2)v, CO or (CJK)m;

J, K = H, 1-6C alkyl-COOH, 1-6C alkyl or 3-6C carbocycle (optionally substituted by one or more of COOH and 1-4C alkoxy);

or CJK = 3-8 membered carbocyclic or heterocyclic ring;

R1 = H, (1-4C) alkoxycarbonyl, 1-4C alkoxy or OH;

R2 = H or 1-4C alkyl;

j = 1-5;

m = 0-10;

r = 0 or 1;

t = 1-5;

v = 0-6;

provided that if Ar = benzofuran, then r is not 0 and X is not (CH2)m.

ACTIVITY - Antiinflammatory; antiasthmatic; antiallergic; antirheumatic; antiarthritic; dermatological; neuroprotective; ophthalmological; gastrointestinal-gen.; immunosuppressive; osteopathic; antiulcer; cardiovascular-gen.

MECHANISM OF ACTION - Tryptase inhibitor. 1,6-bis-(4-(4-Carbamimidoyl-benzene carbonylamino)methyl)-phenoxy) hexane (Ia) inhibited tryptase with a Ki value of below 0.00001 mu M and was less active against trypsin (Ki = 1.3 mu M), thrombin, plasmin, **elastase**, cathepsin G and chymotrypsin (Ki = 100 mu M).

USE - (I) can be used for preventing an inflammatory response and for treating mast cell mediated diseases or diseases involving tryptase activation, specifically asthma, allergic rhinitis, rheumatoid arthritis, dermatological diseases, **multiple sclerosis**, conjunctivitis, inflammatory bowel disease, anaphylaxis, osteoarthritis, peptic ulcers or cardiovascular disease (all claimed).

(I) are especially used for treating asthma, but may also be used for treating e.g. chronic obstructive pulmonary disease, respiratory syncytial virus, smoker's emphysema, urticaria, angioedema, eczematous dermatitis, psoriasis or scleroderma.

Dwg.0/0

L9 ANSWER 11 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-388475 [33] WPIDS
DOC. NO. NON-CPI: N1999-291110
DOC. NO. CPI: C1999-114643
TITLE: Anti-human **medullasin** monoclonal anti-body for sclerosis patients - useful for diagnosing human **medullasin** in blood.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): AOKI, Y; KATSURAGI, H; SUZUKI, H; TAKAHASHI, K
PATENT ASSIGNEE(S): (DAIC) DAINICHISEIKA COLOR & CHEM MFG CO LTD
COUNTRY COUNT: 2
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 11151085	A	19990608	(199933)*		7
CA 2281262	A1	20010228	(200120)#	EN	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 11151085	A	JP 1997-336303	19971120
CA 2281262	A1	CA 1999-2281262	19990831

PRIORITY APPLN. INFO: JP 1997-336303 19971120; CA 1999-2281262 19990831
AN 1999-388475 [33] WPIDS
AB JP 11151085 A UPAB: 19990819
NOVELTY - Anti-human **medullasin** monoclonal anti-body identifies the human **medullasin** existing in granulocytes.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the anti-body manufacturing method. Antibody forming cell and myeloma cell extracted from an animal which is immune to human

medullasin is fused to form hybridoma which is cultured. Antibody is then extracted from the culture.

USE - The labeled antibody is fixed in an insoluble carrier. The sample containing human **medullasin** is contacted with the carrier, when the human **medullasin** is caught on the carrier. The labeled complex is then assayed (claimed). For inflammatory diseases like **multiple sclerosis**.

ADVANTAGE - The immunological assay of human **medullasin** is carried out quickly and easily.

Dwg.0/2

L9 ANSWER 12 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-531911 [45] WPIDS
DOC. NO. CPI: C1998-159623
TITLE: Novel cyclic thio substituted acyl-amino acid amide derivatives - used for treating inflammatory conditions, rheumatoid arthritis and tumours.
DERWENT CLASS: B05
INVENTOR(S): FINK, C A
PATENT ASSIGNEE(S): (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH
COUNTRY COUNT: 82
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9842662	A1	19981001	(199845)*	EN	25
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
AU 9870372	A	19981020	(199909)		
NO 9904482	A	19990916	(200001)		
EP 966439	A1	19991229	(200005)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE SI					
CZ 9903325	A3	19991215	(200007)		
US 6034136	A	20000307	(200019)		
BR 9808030	A	20000308	(200026)		
SK 9901275	A3	20000313	(200032)		
CN 1251092	A	20000419	(200036)		
MX 9908527	A1	19991201	(200110)		
US 6201133	B1	20010313	(200120)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 9842662	A1		WO 1998-EP1584	19980318
AU 9870372	A		AU 1998-70372	19980318
NO 9904482	A		WO 1998-EP1584	19980318
			NO 1999-4482	19990916
EP 966439	A1		EP 1998-917000	19980318
			WO 1998-EP1584	19980318
CZ 9903325	A3		WO 1998-EP1584	19980318
			CZ 1999-3325	19980318
US 6034136	A	Provisional	US 1997-39845	19970320
			US 1998-40093	19980317
BR 9808030	A		BR 1998-8030	19980318
			WO 1998-EP1584	19980318
SK 9901275	A3		WO 1998-EP1584	19980318
			SK 1999-1275	19980318
CN 1251092	A		CN 1998-803485	19980318
MX 9908527	A1		MX 1999-8527	19990917
US 6201133	B1	Provisional	US 1997-39845	19970320
		Div ex	US 1998-40093	19980317
			US 1999-435550	19991108

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9870372	A	Based on	WO 9842662
EP 966439	A1	Based on	WO 9842662
CZ 9903325	A3	Based on	WO 9842662
BR 9808030	A	Based on	WO 9842662
US 6201133	B1	Div ex	US 6034136

PRIORITY APPLN. INFO: US 1997-39845 19970320; US 1998-40093 19980317; US 1999-435550 19991108

AN 1998-531911 [45] WPIDS

AB WO 9842662 A UPAB: 20000718

Novel cyclic thio substituted acylaminoacid amide derivatives of formula (I) and their salts or disulphides corresponding to (I) when R4 = H, are claimed, where R = H, lower alkyl, cycloalkyl, bicycloalkyl, adamantyl, aryl, biaryl, or mono- or di-(cycloalkyl, aryl or biaryl)-lower alkyl, di(lower alkyl or aryl-lower alkyl)amino-lower alkyl, or (piperidino, morpholino, pyrrolidino)-lower alkyl; R1 = H, lower alkyl, cycloalkyl, aryl, biaryl or (cycloalkyl, aryl or biaryl)-lower alkyl; R2 = H, lower alkyl, lower alkoxy, aryl-lower alkyl, aryl-lower alkoxy, amino, mono- or di-(lower alkyl or aryl-lower alkyl)-amino, acylamino or (lower alkyl or aryl-lower alkyl)-(thio, sulphinyl or sulphonyl); R3 = H, lower alkyl, cycloalkyl, aryl-lower alkyl, cycloalkyl-lower alkyl or 2-7C alkyl intercepted by S, SO, SO2, O or NR5; R4 = H or

acyl; R5 = H, lower alkyl, aryl-lower alkyl, acyl or (lower alkyl, aryl or aryl-lower alkyl)-sulphonyl; A = (CH2)p optionally interrupted by S, SO, SO2, O or NR5; n = 0-4; and p = 2-6.

USE - (I) inhibit matrix degradation and are useful for the treatment of galactinase-, stromelysin-, collagenase-, TNF alpha -, MT-MMP-1 and 2- and macrophage metallo-**elastase**-dependent pathological conditions. Such conditions include malignant and non-malignant tumours, such tumours including e.g. breast, lung, bladder, colon and skin cancer. Other conditions to be treated include rheumatoid arthritis, osteoarthritis, bronchial disorders (such as asthma), atherosclerotic conditions, heart attacks, vascular ulcerations, **multiple sclerosis**, optic neuritis, tissue ulceration, bone disease, septic shock, inflammatory bowel disease, Crohn's disease, keratitis, open angleglaucoma, retinopathy and endometriosis. (I) are particularly useful for treating inflammatory conditions, osteoarthritis, rheumatoid arthritis and tumours.

Dwg.0/0

L9 ANSWER 13 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-007430 [01] WPIDS
CROSS REFERENCE: 1995-366143 [47]; 2001-079711 [05]
DOC. NO. CPI: C1998-002549
TITLE: New N-pyrimidinyl- aspartic acid methyl ketone and aldehyde derivatives - used as selective interleukin-1-beta converting enzyme inhibitors, e.g. for treating infectious, inflammatory or auto-immune diseases.
DERWENT CLASS: B03
INVENTOR(S): CHATURVEDULA, P V; DOLLE, R E; PROUTY, C P; SCHMIDT, S J
PATENT ASSIGNEE(S): (SNFI) SANOFI
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5670494	A	19970923	(199801)*		12

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5670494	A	CIP of	US 1994-221712	19940331
			US 1995-559870	19951120

PRIORITY APPLN. INFO: US 1995-559870 19951120; US 1994-221712

19940331
AN 1998-007430 [01] WPIDS
CR 1995-366143 [47]; 2001-079711 [05]
AB US 5670494 A UPAB: 20010213
The following N-(pyrimidinyl)-aspartic acid substituted methyl ketone and aldehyde analogues (I) are new compounds: (a) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 2,6-dichlorobenzoyl-oxymethyl ketone; (b) N-(2-(5-thiomethyl-benzoylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 2,6-dichlorobenzoyl-oxymethyl ketone; (c) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid diphenyl-phosphin-oxy-methyl ketone; (d) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(1-(4-chlorophenyl)-3-trifluoromethyl)-pyrazoloxy-methyl ketone; (e) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(3-phenyl)-coumarinyl-oxymethyl ketone; (f) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(1-phenyl-3-fluoromethyl)-pyrazol-oxymethyl ketone; (g) N-(2-(5-isopropyloxy-carbonylamino-6-oxo-2-phenyl-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(1-phenyl-3-trifluoromethyl)-pyrazol-oxymethyl ketone; (h) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(3-pyridinyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(1-phenyl-3-trifluoromethyl)-pyrazol-oxymethyl ketone; (i) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(2-thienyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(1-phenyl-3-trifluoromethyl)-pyrazol-oxymethyl ketone; (j) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-methyl-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(1-phenyl-3-trifluoromethyl)-pyrazol-oxymethyl ketone; (k) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(2-thienyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(1-(2-pyridinyl)-3-trifluoromethyl)-pyrazol-oxymethyl ketone; (l) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(2-thienyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 5-(1-(4-chlorophenyl)-3-trifluoromethyl)-pyrazol-oxymethyl ketone; (m) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(2-thienyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid 2,6-dichlorobenzoyl-oxymethyl ketone; and (n) N-(2-(5-benzyloxycarbonylamino-6-oxo-2-(2-thienyl)-1,6-dihydro-1-pyrimidinyl)-acetoyl)-L-aspartic acid aldehyde.

USE - (I) inhibit interleukin-1 beta protease, i.e. interleukin-1 beta converting enzyme (ICE), in vitro and in vivo. ICE-inhibiting pharmaceutical compositions containing (I) are claimed; they are useful for treatment of ICE-mediated disorders such as infectious diseases (e.g. meningitis and salpingitis), complications of infections (e.g. disseminated intravasal coagulation, ARDS and septic shock), respiratory disease,

respiratory diseases, acute or chronic inflammation due to antigen, antibody and/or complement deposition, inflammatory conditions (e.g. arthritis, cholangitis, colitis, encephalitis, endocarditis, hepatitis, glomerulonephritis, myocarditis, pericarditis, pancreatitis, vasculitis and reperfusion injury), immune-based disease (e.g. acute and delayed hypersensitivity, graft-versus-host disease and graft rejection), autoimmune diseases (e.g. Type I diabetes and **multiple sclerosis**), bone diseases and certain tumours and leukaemias. (I) are particularly useful for treating rheumatoid arthritis. They can also be used as research tools in pharmacological, diagnostic and related studies.

ADVANTAGE - (I) are non-peptide compounds (having enhanced bioavailability compared with peptides) having potent and selective ICE inhibiting activity. (I) do not inhibit human leukocyte **elastase**.

Dwg.0/0

L9 ANSWER 14 OF 21 SCISEARCH COPYRIGHT 2001 ISI (R)

ACCESSION NUMBER: 97:751966 SCISEARCH

THE GENUINE ARTICLE: XZ469

TITLE: Neutral proteases and disruption of the blood-brain barrier in rat

AUTHOR: Armao D; Kornfeld M; Estrada E Y; Grossetete M; Rosenberg G A (Reprint)

CORPORATE SOURCE: UNIV NEW MEXICO, DEPT NEUROL, ALBUQUERQUE, NM 87131 (Reprint); UNIV NEW MEXICO, DEPT NEUROL, ALBUQUERQUE, NM 87131; UNIV NEW MEXICO, DEPT PATHOL NEUROPATHOL, ALBUQUERQUE, NM 87131

COUNTRY OF AUTHOR: USA

SOURCE: BRAIN RESEARCH, (5 SEP 1997) Vol. 767, No. 2, pp. 259-264.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0006-8993.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Blood-brain barrier disruption is common in many neurological diseases. Matrix metalloproteinases are induced in brain injury and increase capillary permeability by attacking the extracellular matrix around cerebral capillaries. Other neutral proteases are also increased in sites of secondary injury, and may contribute to the proteolysis of the blood-brain barrier. Therefore, we studied capillary permeability and histological tissue damage after intracerebral injection of neutrophil **elastase**, cathepsin G, heparatinase and plasmin. Adult rats were injected

intracerebrally with an enzyme. After 1, 4 or 24 h, measurements were made of brain uptake of a radiolabeled tracer, [C-14]sucrose. Enzymes that significantly increased capillary permeability were injected into other rats for histological assessment of tissue damage. **Elastase** increased capillary permeability significantly when compared with controls; maximal damage was seen at 4 h. Plasmin produced smaller increases in permeability at 4 h, exerting its maximal effect on sucrose uptake at 24 h. Cathepsin G had a small effect at 4 h. Heparitinase had no effect. Histologic examination of **elastase**-injected brains at 24 h revealed multifocal perivascular and intraparenchymal acute hemorrhages accompanied by a polymorphonuclear cell infiltrate. **Elastase** -injected brains were microscopically similar to saline-injected brains at 1 and 4 h. Plasmin produced fibrinoid changes in the blood vessels at 24 h, coinciding with the maximal increase in capillary permeability. We conclude that neutrophil **elastase** attacks the capillary extracellular matrix, causing extensive hemorrhage, while plasmin leads to increased vascular permeability and fibrinoid necrosis of blood vessel walls. Differential effects of neutral proteases released secondary to injury could be important in both the acute changes in blood vessel permeability and long-term alterations in vessel structure. (C) 1997 Elsevier Science B.V.

L9 ANSWER 15 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1997-077260 [07] WPIDS
DOC. NO. CPI: C1997-024782
TITLE: New mercapto amide cpds. e.g. 2-isobutyl-4-oxo-5-mercapto pentanoyl-(L)-beta-cyclohexyl alanine phenethyl amide - used as matrix metalloprotease inhibitors for treating tissue breakdown or inflammatory conditions e.g. rheumatoid arthritis, bone resorption and Crohn's disease.
DERWENT CLASS: B03 B05 D21
INVENTOR(S): CAMPBELL, D A; PATEL, D V; XIAO, X Y; XIAO, X
PATENT ASSIGNEE(S): (AFFY-N) AFFYMAX TECHNOLOGIES NV
COUNTRY COUNT: 72
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9640738	A1	19961219	(199707)*	EN	97
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN					
AU 9662699	A	19961230	(199716)		

EP 832100 A1 19980401 (199817) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 5831004 A 19981103 (199851)
AU 700239 B 19981224 (199912)
US 5929278 A 19990727 (199936)
EP 832100 B1 20000405 (200021) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
DE 69607615 E 20000511 (200030)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9640738	A1		WO 1996-US9932	19960606
AU 9662699	A		AU 1996-62699	19960606
EP 832100	A1		EP 1996-921482	19960606
			WO 1996-US9932	19960606
US 5831004	A	CIP of	US 1994-329420	19941027
		CIP of	US 1995-484255	19950607
			US 1995-549345	19951027
AU 700239	B		AU 1996-62699	19960606
US 5929278	A	CIP of	US 1994-329420	19941027
		CIP of	US 1995-484255	19950607
		Cont of	US 1995-549345	19951027
			US 1998-81466	19980519
EP 832100	B1		EP 1996-921482	19960606
			WO 1996-US9932	19960606
DE 69607615	E		DE 1996-607615	19960606
			EP 1996-921482	19960606
			WO 1996-US9932	19960606

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9662699	A	Based on	WO 9640738
EP 832100	A1	Based on	WO 9640738
AU 700239	B	Previous Publ.	AU 9662699
		Based on	WO 9640738
US 5929278	A	Cont of	US 5831004
EP 832100	B1	Based on	WO 9640738
DE 69607615	E	Based on	EP 832100
		Based on	WO 9640738

PRIORITY APPLN. INFO: US 1995-549345 19951027; US 1995-484255 19950607; US 1994-329420 19941027; US 1998-81466 19980519
AN 1997-077260 [07] WPIDS

Searcher : Shears 308-4994

AB WO 9640738 A UPAB: 19970212
Amido-substd. mercaptoalcohol or mercaptoketone derivs. of formulae (I)-(III) and their salts are new. A = CO or CHOH; M, Q = H, opt. substd. alkyl, aryl or heteroaryl; R = NR1R2 or NHCHQ'CONR1R2; R1 = H, opt. substd. alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; R2 = H; or NR1R2 = heterocyclic or heteroaryl ring; Q' = as Q; R3 = -(CH2)n-V; n = 0-4; V = H, opt. substd. alkyl, OR13, NR12R13 or SR13; R12, R13 = H, opt. substd. alkyl, alkenyl, aryl, aralkyl, opt. substd. alkanoyl, aroyl, heteroaroyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroaralkyl; or NR12R13 = heteroaryl or heterocyclic ring; m = 0-2.

USE - (I)-(III) are inhibitors of metalloproteases, esp. matrix metalloproteases (e.g. stromelysins, collagenases, **elastases**, matrilysin and gelatinases, but not stromelysin-I or collagenase-1). They are used for treating or controlling disease states associated with metalloproteases (other than stromelysin-I and collagenase-1) or involving tissue breakdown and inflammatory conditions (all claimed). Conditions treated include e.g. osteoarthritis, rheumatoid arthritis, septic arthritis, articular cartilage degradation, tumour invasion in certain cancers, periodontal disease, dermatological conditions, bone resorption, arthropathy, corneal ulcerations, proteinuria, dystrophobic epidermolysis bullosa, coronary thrombosis associated with atherosclerotic plaque rupture, aneurysmal aortic disease, Crohn's disease, **multiple sclerosis** and cachexia associated with cancer or HIV infection. (I)-(III) also promote wound healing; inhibit metalloproteases involved in pathways of disease states (e.g. ACE, neural endopeptidase or TNF-alpha processing metalloenzyme); and may be effective as birth control agents.
Dwg.1/16

L9 ANSWER 16 OF 21 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 96:813128 SCISEARCH
THE GENUINE ARTICLE: VQ440
TITLE: SCLERAL MATRIX METALLOPROTEINASES, SERINE PROTEINASE ACTIVITY AND HYDRATIONAL CAPACITY ARE INCREASED IN MYOPIA INDUCED BY RETINAL IMAGE DEGRADATION
AUTHOR: JONES B E; THOMPSON E W; HODOS W; WALDBILLIG R J; CHADER G J (Reprint)
CORPORATE SOURCE: NEI, RETINAL CELL & MOL BIOL LAB, NIH, BLDG 6, ROOM 310, 6 CTR DR MSC 2740, BETHESDA, MD, 20892 (Reprint); NEI, RETINAL CELL & MOL BIOL LAB, NIH, BETHESDA, MD, 20892; GEORGETOWN UNIV, SCH MED, DEPT CELL BIOL, WASHINGTON, DC, 20007; GEORGETOWN UNIV, SCH MED, VINCENT T LOMBARDI CANC RES CTR, WASHINGTON, DC, 20007; GEORGETOWN UNIV, SCH MED,

DEPT ORTHOPED SURG, WASHINGTON, DC, 20007; UNIV MARYLAND, DEPT PSYCHOL, COLLEGE PK, MD, 20742
COUNTRY OF AUTHOR: USA
SOURCE: EXPERIMENTAL EYE RESEARCH, (OCT 1996) Vol. 63, No. 4, pp. 369-381.
ISSN: 0014-4835.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the avian model of myopia, retinal image degradation quickly leads to ocular enlargement. We now give evidence that, regionally specific changes in ocular size are correlated with both biomechanical indices of scleral remodeling, e.g. hydration capacity and with biochemical changes in proteinase activities. The latter include a 72 kDa matrix metalloproteinase (putatively MMP-2), other gelatin-binding MMPs, an acid pH MMP and a serine protease. Specifically, we have found that increases in scleral hydrational capacity parallel increases in collagen degrading activities. Gelatin zymography reveals that eyes with 7 days of retinal image degradation have elevated levels (1.4-fold) of gelatinolytic activities at 72 and 67 kDa M(r) in equatorial and posterior pole regions of the sclera while, after 14 days of treatment, increases are no longer apparent. Lower M(r) zymographic activities at 50, 46 and 37 kDa M(r) are collectively increased in eyes treated for both 7 and 14 days (1.4- and 2.4-fold respectively) in the equator and posterior pole areas of enlarging eyes. Western blot analyses of scleral extracts with an antibody to human MMP-2 reveals immunoreactive bands at 65, 30 and 25 kDa. Zymograms incubated under slightly acidic conditions reveal that, in enlarging eyes, MMP activities at 25 and 28 kDa M(r) are increased in scleral equator and posterior pole (1.6- and 4.5-fold respectively). A TIMP-like protein is also identified in sclera and cornea by Western blot analysis. Finally, retinal-image degradation also increases (similar to 2.6-fold) the activity of a 23.5 kDa serine proteinase in limbus, equator and posterior pole sclera that is inhibited by aprotinin and soybean trypsin inhibitor. Taken together, these results indicate that eye growth induced by retinal-image degradation involves increases in the activities of **multiple scleral** proteinases that could modify the biomechanical properties of scleral structural components and contribute to tissue remodeling and growth. (C) 1996 Academic Press Limited

L9 ANSWER 17 OF 21 JICST-EPlus COPYRIGHT 2001 JST
ACCESSION NUMBER: 900911580 JICST-EPlus
TITLE: Scaleroderma (progressive systemic scaleroderma).
AUTHOR: SHIOSAKA TAKAHIKO

CORPORATE SOURCE: Ehimeken'iryogitandai
SOURCE: Rinsho to Kenkyu (Japanese Journal of Clinical and Experimental Medicine), (1990) vol. 67, no. 10, pp. 3177-3178. Journal Code: Z0376B
ISSN: 0021-4965
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Commentary
LANGUAGE: Japanese
STATUS: New

L9 ANSWER 18 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89180247 EMBASE
DOCUMENT NUMBER: 1989180247
TITLE: [PMN-**elastase** in the CSF. Diagnostic value in acute flammatory diseases of the central nervous system].
PMN-**ELASTASE** IM LIQUOR IN DER DIAGNOSTIK AKUT ENTZUNDLICHER ZNS-ERKRANKUNGEN.
AUTHOR: Stoffler A.; Baas H.; Fischer P.-A.
CORPORATE SOURCE: Abteilung fur Neurologie, Universitats-Klinik, D-6000 Frankfurt/Main, Germany
SOURCE: Nervenarzt, (1989) 60/7 (420-424).
ISSN: 0028-2804 CODEN: NERVAF
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: German

L9 ANSWER 19 OF 21 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 89209254 MEDLINE
DOCUMENT NUMBER: 89209254 PubMed ID: 3072117
TITLE: Enzyme immunoassay of **medullasin** in peripheral blood.
AUTHOR: Aoki Y; Yoshida M; Kominami E
CORPORATE SOURCE: Department of Biochemistry and Nutrition, Institute of Public Health, Tokyo, Japan.
SOURCE: CLINICA CHIMICA ACTA, (1988 Dec 15) 178 (2) 193-204.
Journal code: DCC; 1302422. ISSN: 0009-8981.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198905
ED Entered STN: 19900306
Last Updated on STN: 20000303
Entered Medline: 19890526
AB An enzyme immunoassay method for the determination of the amount of

medullasin, a serine protease in granulocytes, was developed. Beads coated with IgG obtained from immunized rabbits were incubated with **medullasin**, Fab'-peroxidase conjugate was added, and peroxidase activity bound to beads was measured by a fluorophotometer. The amount of **medullasin** determined by this method correlated well with the value calculated from the protease activity measured by the conventional method. The minimum detectable amount of **medullasin** was 300 pg. Granulocytes obtained from patients with **multiple sclerosis** in active phase and those from patients with Behcet's disease in relapse showed elevated levels of **medullasin** as compared with normal controls. However, the amount of **medullasin** in granulocytes obtained from patients in remission revealed normal values. These results indicate that elevated levels of **medullasin** activity in granulocytes of these diseases in relapse is due to an increased amount of **medullasin** in granulocytes and that the normalization of **medullasin** activity in remission is the result of the decrease of the amount of **medullasin** in granulocytes.

L9 ANSWER 20 OF 21 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 84201631 MEDLINE
DOCUMENT NUMBER: 84201631 PubMed ID: 6372647
TITLE: **Medullasin** activity in granulocytes of patients with **multiple sclerosis**.
AUTHOR: Aoki Y; Miyatake T; Shimizu N; Yoshida M
SOURCE: ANNALS OF NEUROLOGY, (1984 Mar) 15 (3) 245-9.
Journal code: 6AE; 7707449. ISSN: 0364-5134.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198406
ED Entered STN: 19900319
Last Updated on STN: 20000303
Entered Medline: 19840611

AB **Medullasin** activity in mature granulocytes was measured in the blood of 22 patients with **multiple sclerosis** (definite type, 16; probable type, 6). The activity was elevated in every patient in relapse; it decreased to nearly normal levels at the beginning of improvement and further decreased to normal levels with remission. Serial determinations of the level of **medullasin** activity in 3 patients revealed that activity increased several days before the onset of acute exacerbation. **Medullasin** activity level in mature granulocytes obtained from patients with neurological diseases other than **multiple sclerosis** was largely within the normal range, except in 2 patients with spinocerebellar degeneration. Measurement of

medullasin activity in mature granulocytes may become useful in both diagnosis and evaluation of **multiple sclerosis**.

L9 ANSWER 21 OF 21 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 84111890 MEDLINE
DOCUMENT NUMBER: 84111890 PubMed ID: 6198330
TITLE: Differential isoelectric focusing properties of crude and purified human alpha 2-macroglobulin and alpha 2-macroglobulin-proteinase complexes.
AUTHOR: Back S A; Alhadeff J A
CONTRACT NUMBER: AM 01107 (NIADDK)
AM 20409 (NIADDK)
SOURCE: JOURNAL OF CHROMATOGRAPHY, (1983 Nov 11) 278 (1) 43-51.
Journal code: HQF; 0427043. ISSN: 0021-9673.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198402
ED Entered STN: 19900319
Last Updated on STN: 20000303
Entered Medline: 19840229

AB The isoelectric focusing (IEF) properties of human alpha 2-macroglobulin (alpha 2M) and alpha 2M-proteinase complexes from crude and partially purified preparations were studied by column IEF. The average isoelectric point (pI) of the major form was 6.5 for alpha 2M from crude plasma but was 5.3 for purified samples. Following preincubation with either trypsin, chymotrypsin or pancreatic **elastase** the crude alpha 2M-proteinase complexes displayed pI values ranging from 5.3 to 6.1 and the purified alpha 2M-proteinase complexes ranged from pH 6.0 to 6.1. A comparison of recoveries for focused crude or purified alpha 2M and trypsin-preincubated alpha 2M indicated enhanced recovery for the trypsin-preincubated samples suggesting that the binding of the proteinase enhances the stability of alpha 2M. alpha 2M thus displays column IEF properties which appear to be dependent upon the state of purity of the molecule. These findings are of particular significance to investigators concerned with using expressions of altered alpha 2M electrophoretic patterns for clinical diagnostic purposes in such diseases as **multiple sclerosis**, diabetes and cystic fibrosis.

(FILE 'MEDLINE' ENTERED AT 14:43:04 ON 23 APR 2001)
L10 547 SEA FILE=MEDLINE ABB=ON PLU=ON "MATRIX METALLOPROTEINASES"/CT
L11 18616 SEA FILE=MEDLINE ABB=ON PLU=ON "MULTIPLE SCLEROSIS"/CT

L12 6 SEA FILE=MEDLINE ABB=ON PLU=ON L10 AND L11

L12 ANSWER 1 OF 6 MEDLINE
AN 2001202742 MEDLINE
TI Immunological markers in multiple sclerosis.
AU Gironi M; Bergami A; Brambilla E; Ruffini F; Furlan R; Comi G; Martino G
SO NEUROLOGICAL SCIENCES, (2000) 21 (4 Suppl 2) S871-5. Ref: 22
Journal code: DRB. ISSN: 1590-1874.
AB Multiple sclerosis (MS) is characterized by the presence in the central nervous system (CNS) of perivascular inflammatory infiltrates containing, among others, autoreactive T cells and activated macrophages. These observations indicate that MS is a T cell-mediated CNS-confined chronic inflammatory demyelinating disease in which the ultimate effector cell is the activated macrophage. The inflammatory process, leading to patchy demyelination and axonal loss, is mainly sustained by pro-inflammatory cytokines that, along with chemokines, adhesion molecules and metalloproteases, modulate at different levels the pathogenic process underlying MS. Due to their central role in MS pathogenesis, "inflammatory" molecules might represent suitable peripheral markers of disease (disease-trait) and/or disease activity (state-trait). However, reliable disease-trait or state-trait immunological markers for MS have not yet been identified. The intrinsic characteristics of these molecules (i.e. autocrine/paracrine activity, short half-life, redundancy) may in part explain their inconsistency as disease markers. Additionally, the unreliability of methodologies and the lack of careful patient stratification can also, at least in part, account for the unsatisfactory results so far obtained.

L12 ANSWER 2 OF 6 MEDLINE
AN 2001196421 MEDLINE
TI Matrix metalloproteinases and tissue inhibitors of metalloproteinases in cerebrospinal fluid differ in multiple sclerosis and Devic's neuromyelitis optica.
AU Mandler R N; Dencoff J D; Midani F; Ford C C; Ahmed W; Rosenberg G A
SO BRAIN, (2001 Mar) 124 (Pt 3) 493-8.
Journal code: B5F. ISSN: 0006-8950.
AB Matrix metalloproteinases (MMPs) are increased in the CSF of patients with multiple sclerosis. Devic's neuromyelitis optica (DNO) is a demyelinating syndrome that involves the optic nerve and cervical cord but differs pathologically from multiple sclerosis. Therefore, we hypothesized that the type of inflammatory reaction that causes MMPs to be elevated in multiple sclerosis would be absent in patients with DNO. CSF was collected from 23 patients with relapsing-remitting or secondary progressive multiple sclerosis, all

of whom were experiencing acute symptoms, from seven patients with DNO, and from seven normal volunteers. Diagnoses were made according to current criteria on the basis of clinical manifestations, imaging results and CSF studies. IgG synthesis was increased in the CSF of multiple sclerosis patients but not in that of DNO patients. Zymography, reverse zymography and ELISA (enzyme-linked immunosorbent assay) were used to measure gelatinase A (MMP-2), gelatinase B (MMP-9) and tissue inhibitors of metalloproteinases (TIMPs). Zymograms showed that multiple sclerosis patients had elevated MMP-9 compared with DNO patients and controls (P: < 0.05). TIMP-1 and TIMP-2 levels were similar in all three groups. We conclude that multiple sclerosis patients have higher MMP-9 levels in the CSF than patients with DNO, which supports the different pathological mechanisms of these diseases.

L12 ANSWER 3 OF 6 MEDLINE
AN 2000434088 MEDLINE
TI [The evidence for primary axonal loss in multiple sclerosis]. Evidencias en favor de una perdida axonal primaria en la esclerosis multiple.
AU Anthony D C; Hughes P; Perry V H
SO REVISTA DE NEUROLOGIA, (2000 Jun 16-30) 30 (12) 1203-8. Ref: 52 Journal code: CG9; 7706841. ISSN: 0210-0010.
AB INTRODUCTION: At what stage in the pathogenesis of multiple sclerosis (MS) does the damage to axons occur, and why should there be any axon loss at all in what is thought to be principally an axon sparing demyelinating disease? A recently described new technique for investigating axon damage depends for its ability on the immunoreactivity of amiloid precursor protein (APP), which has been shown to be more sensitive than silver stains for detecting damaged axons. DEVELOPMENT: We used APP immunoreactivity as a method to investigate whether axon damage occurs in acute MS lesions. The results of our APP staining showed that the expression of APP in MS lesions is associated with acute MS lesions and the active border of less acute lesions. There was little, if any, APP expression in the chronic lesions. If we accept that the APP staining represents irreversible damage to some axons, the next question is what factors are responsible for mediating damage to axons in MS? Matrix metalloproteinases (MMP) are expressed by macrophages in acute MS lesions and in the active borders of active chronic lesions. The injection of highly-purified MMP into the brain results in demyelination, blood-brain barrier breakdown, and axonal loss. Moreover, the inhibition of the MMP activity reduces the severity of MS-like lesions in experimental models. Thus the properties and distribution of these enzymes make them rational targets for therapeutic intervention. CONCLUSION: Whatever mechanism proves to be responsible for axonal damage in MS, it is clear that this disease should, perhaps, be more appropriately recognized as a

primary demyelinating entity with associated primary axonal loss.

L12 ANSWER 4 OF 6 MEDLINE
AN 2000413209 MEDLINE
TI Multiple sclerosis: pro- and anti-inflammatory cytokines and metalloproteinases are affected differentially by treatment with IFN-beta.
AU Ozenci V; Kouwenhoven M; Teleshova N; Pashenkov M; Fredrikson S; Link H
SO JOURNAL OF NEUROIMMUNOLOGY, (2000 Aug 1) 108 (1-2) 236-43. Journal code: HSO; 8109498. ISSN: 0165-5728.
AB Interferon-beta (IFN-beta) has a beneficial influence on the course of multiple sclerosis (MS) and has become standard treatment of this disease, though its mechanisms of action are incompletely understood. This study examines the effect of IFN-beta treatment on the cytokines IL-6, TNF-alpha, IFN-gamma and IL-10; the metalloproteinases MMP-3, -7 and -9 and the tissue inhibitor of metalloproteinase-1 (TIMP-1). IFN-beta treatment resulted in decreased numbers of mononuclear cells (MNC) secreting IL-6 and TNF-alpha and expressing mRNA of MMP-3 and MMP-9 compared to pretreatment levels. On the contrary, numbers of IL-10 secreting MNC and TIMP-1 mRNA expressing were augmented during IFN-beta therapy. Whether the down-regulatory effects on pro-inflammatory and upregulatory effects on anti-inflammatory molecules are a direct result of IFN-beta on the immune system or secondary to clinical stabilization of MS pathology induced by IFN-beta remains to be evaluated.

L12 ANSWER 5 OF 6 MEDLINE
AN 2000314619 MEDLINE
TI The role of matrix metalloproteinases in autoimmune damage to the central and peripheral nervous system.
AU Hartung H P; Kieseier B C
SO JOURNAL OF NEUROIMMUNOLOGY, (2000 Jul 24) 107 (2) 140-7. Ref: 60 Journal code: HSO; 8109498. ISSN: 0165-5728.
AB Members of the family of matrix metalloproteinases (MMPs) have been implicated in the pathogenesis of inflammatory demyelination. MMPs apparently mediate important steps in the genesis of inflammatory demyelination, such as cell migration, blood-brain/nerve barrier breakdown, demyelination, and cytokine activation. This review will highlight in vitro as well as in vivo findings, which support the importance of this group of proteases in the pathogenesis of inflammatory demyelinating disorders of the central and peripheral nervous system.

L12 ANSWER 6 OF 6 MEDLINE
AN 2000158282 MEDLINE
TI Molecular pathogenesis of multiple sclerosis.

AU Bar-Or A; Oliveira E M; Anderson D E; Hafler D A
SO JOURNAL OF NEUROIMMUNOLOGY, (1999 Dec) 100 (1-2) 252-9. Ref: 97
Journal code: HSO; 8109498. ISSN: 0165-5728.
AB Multiple sclerosis (MS) is best understood as an inflammatory disease of the central nervous system (CNS) white matter characterized by demyelination, focal T cell and macrophage infiltrates, axonal injury and loss of neurological function. Our current understanding invokes proinflammatory cells and mediators that may be triggered by environmental factors to mediate disease in a genetically susceptible host. Five major themes which have been associated with the pathogenesis of MS lesions will be discussed: (1) The differential activation states of myelin-reactive T cells from MS patients vs. normal individuals, (2) the selective expression of chemokines, adhesion molecules and matrix metalloproteinases, (3) the proposed roles of the B7 costimulatory pathway, (4) the proinflammatory cytokines and (5) the role of molecular mimicry.

FILE 'CAPLUS' ENTERED AT 14:47:20 ON 23 APR 2001
L13 79 S MMP(2A)12
L14 2 S L13 AND (MS(S)SCLER? OR MULTIPLE SCLER?)
L15 0 S L14 NOT L7

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 14:49:22 ON 23 APR 2001)
L16 13 S L14
L17 10 S L16 NOT L8
L18 7 DUP REM L17 (3 DUPLICATES REMOVED)

L18 ANSWER 1 OF 7 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:303518 SCISEARCH
THE GENUINE ARTICLE: 419HC
TITLE: Production of MMPs in human cerebral endothelial cells and their role in shedding adhesion molecules
AUTHOR: Hummel V (Reprint); Kallmann B A; Wagner S; Fuller T; Bayas A; Tonn J C; Benveniste E N; Toyka K V; Rieckmann P
CORPORATE SOURCE: Univ Wurzburg, Dept Neurol, Clin Res Unit Multiple Sclerosis & Neuroimmunol, Josef Schneider Str 11, D-97080 Wurzburg, Germany (Reprint); Univ Wurzburg, Dept Neurol, Clin Res Unit Multiple Sclerosis & Neuroimmunol, D-97080 Wurzburg, Germany; Univ Wurzburg, Dept Neurosurg, D-97080 Wurzburg, Germany; Univ Alabama, Dept Cell Biol, Birmingham, AL USA
COUNTRY OF AUTHOR: Germany; USA
SOURCE: JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY (APR 2001) Vol. 60, No. 4, pp. 320-327. Publisher: AMER ASSN NEUROPATHOLOGISTS INC, 1041 NEW

HAMPSHIRE ST, LAWRENCE, KS 66044 USA.
ISSN: 0022-3069.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 48

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Matrix metalloproteinases (MMPs) are Zn2+-endopeptidases that seem to play an important role in chronic inflammatory diseases of the central nervous system by disrupting the blood-brain barrier (BBB) and mediating the destruction of myelin components. We therefore investigated the influence of the pro-inflammatory cytokine TNF-alpha on the expression and activation of several MMPs in human cerebral endothelial cells (HCEC). HCEC constitutively express MMP-2 and MMP-3 mRNA, but only MMP-3 is upregulated on mRNA and protein level after TNF-alpha stimulation. MMP-9 and **MMP -12** mRNA could only be detected under inflammatory conditions. Furthermore, MMPs are involved in shedding of cell surface molecules. We therefore investigated the influence of MMPs on the release of soluble adhesion molecules using marimastat, a specific broad-spectrum MMP inhibitor and other protease inhibitors like aprotinin or leupeptin. Only marimastat inhibited the TNF-alpha mediated release of sVCAM-1 in the supernatants of HCEC. Western blot results of culture supernatants supported the time dependent release of the complete extracellular portion of the VCAM-1 molecule. These data suggest that MMPs produced by HCEC are actively involved in the shedding of soluble adhesion molecules at the BBB.

L18 ANSWER 2 OF 7 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:236959 SCISEARCH
THE GENUINE ARTICLE: 410CB
TITLE: Interleukin 15 stimulates production of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 by human peripheral blood mononuclear cells
AUTHOR: Constantinescu C S (Reprint); Grygar C; Kappos L; Leppert D
CORPORATE SOURCE: Univ Nottingham Hosp, Queens Med Ctr, Div Clin Neurol, Med Sch Bldg, B Floor, Nottingham NG7 2UH, England (Reprint); Univ Nottingham Hosp, Queens Med Ctr, Div Clin Neurol, Nottingham NG7 2UH, England; Univ Hosp, Dept Neurol, Basel, Switzerland; Univ Hosp, Dept Res, Basel, Switzerland
COUNTRY OF AUTHOR: England; Switzerland
SOURCE: CYTOKINE, (21 FEB 2001) Vol. 13, No. 4, pp. 244-247. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 1043-4666.

DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 15
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In peripheral blood mononuclear cells (PBMC), matrix metalloproteinase (MMP)-9 mediates the extravasation of immune cells and may be involved in tissue destruction during inflammation. We investigated the effect of the pro-inflammatory cytokines interleukin (IL-)12 and 15 on the secretion of MMP-9 in PBMC, IL-15, but not IL-12, induces **MMP**-9 in PBMC and in T cells. Moreover, the combination of IL-15 and IL-2 had an additive effect. In contrast, both IL-12 and IL-15 induced the release of tissue inhibitor of metalloproteinases (TIMP)-1, IL-15 led to a dose-dependent increase of the MMP-9/TIMP-1 ratio as a measure for increased proteolytic capacity, We conclude that IL-15 mediates its effects in inflammation in part through MMP-9. (C) 2001 Academic Press.

L18 ANSWER 3 OF 7 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-465933 [40] WPIDS
DOC. NO. CPI: C2000-140328
TITLE: New pyrrolidine derivatives, useful for the treatment of e.g. neoplasia, emphysema, cardiovascular disorders or **multiple sclerosis**, are matrix metalloproteinase inhibitors.
DERWENT CLASS: B02 B03 C02
INVENTOR(S): FLYNN, G A
PATENT ASSIGNEE(S): (AVET) AVENTIS PHARM INC
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000040553	A1	20000713	(200040)*	EN	73

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 2000019265 A 20000724 (200052)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000040553	A1	WO 1999-US28234	19991130

AU 2000019265 A AU 2000-19265 19991130

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000019265 A	Based on	WO 200040553

PRIORITY APPLN. INFO: US 1998-224456 19981231
AN 2000-465933 [40] WPIDS
AB WO 200040553 A UPAB: 20000823
NOVELTY - Pyrrolidine derivatives (I) are new.
DETAILED DESCRIPTION - Pyrrolidine derivatives of formula (I) are new.
e = 0 - 2;
A = OH or NRR';
R, R' = H or 1-6C alkyl; or
NRR' = N-morpholino, N-piperidino, N-pyrrolidino or N-isoindolyl;
R1 = H, 1-6C alkyl, (CH2)aCO2R5, (CH2)aC(O)NH2, (CH2)4NH2, (CH2)3NHC(NH)NH2, (CH2)2S(O)bCH3, CH2OH, CH(OH)CH3, CH2SH, (CH2)dAr1 or CH2Ar2;
a = 1 or 2;
b = 0 - 2;
d = 0 - 4;
R5 = H, 1-4C alkyl or benzyl;
Ar1 = phenyl substituted by 1 - 2 R6 or naphthyl substituted by R7;
R6 = H, halogen, 1-4C alkyl, OH or 1-4C alkoxy;
R7 = H, halogen, 1-4C alkyl or 1-4C alkoxy;
Ar2 = indol-3-yl or 4-imidazolyl;
R2 = phenyl substituted by 1 - 2 R2' or naphthyl substituted by 1 - 2 R2';
R2' = H, halogen, 1-4C alkyl or 1-4C alkoxy;
R3 = 1-6 alkyl, (CH2)mW', (CH2)pAr3, (CH2)kCO2R9, (CH2)mN(R8')SO2Y1 or (CH2)mZ'Q;
m = 2 - 8;
p = 0 - 10;
k = 1 - 9;
W' = phthalimido;
Ar3 = quinolinyl, imidazolyl, thienyl, furanyl, pyridyl, or phenyl substituted by 1 - 2 R23;
R23 = H, halogen, 1-4C alkyl or 1-4C alkoxy;
R8', R9 = 1-6C alkyl;
Y1 = H, (CH2)jAr4 or N(R24)2;
j = 0 - 1;
R24 = H or 1-6C alkyl; or
NR24R24 = N-morpholino, N-piperidino, N-pyrrolidino or

N-isoindolyl;
Ar4 = phenyl substituted by 1 - 3 R25;
R25 = H, halogen, 1-4C alkyl or 1-4C alkoxy;
Z' = O, NR8, C(O)NR8, NR8C(O), NR8C(O)NH, NR8C(O)O or OC(O)NH;
R8 = H or 1-6C alkyl;
Q = H, (CH2)nY2 or (CH2)xY3;
n = 0 - 4;
Y2 = H, (CH2)hAr5 or (CH2)tC(O)OR27;
Ar5 = quinolinyl or phenyl substituted by 1 - 3 R26;
R26 = H, halogen, 1-4C alkyl or 1-4C alkoxy;
h = 0 - 6;
t = 1 - 6;
R27 = H or 1-6C alkyl;
x = 2 - 4;
Y3 = N(R28)2, N-morpholino, N-piperidino, N-pyrrolidino or N-isoindolyl;
R28 = H or 1-6C alkyl;
R4 = C(O)R10, C(O)(CH2)qK' or SG;
R10 = H, 1-4C alkyl, phenyl, benzyl;
q = 0 - 2;
K' = pyridyl, 1-imidazolyl, NR11R11', phenyl substituted by NR11R11' or a group of formula (i);
V' = bond, CH2, O, S(O)r, NR21 or NC(O)R22;
r = 0 - 2;
R21, R11, R11' = H, 1-4C alkyl or benzyl;
R22 = H, CF3, 1-10C alkyl, phenyl or benzyl;
G = (CH2)w-pyridyl, (CH2)w-phenyl substituted by 1 - 2 R14, pyrid-2-yl or a group of formula (ii) - (v);
w = 1 - 3;
R12 = H, 1-6C alkyl, CH2CH2S(O)fCH3 or benzyl;
f = 0 - 2;
R13 = H, OH, amino, 1-6C alkyl, N-methylamino, N,N-dimethylamino, CO2R17 or OC(O)R18;
R17 = H, CH2OC(O)C(CH3)3, 1-4C alkyl, benzyl or diphenylmethyl;
R18 = H, 1-6C alkyl or phenyl;
R14 = H, 1-4C alkyl, 1-4C alkoxy or halogen;
V1 = O, S or NH;
V2 = N or CH;
V3 = bond or C(O);
V4 = O, S, NR19 or NC(O)R20;
R19 = H, 1-4C alkyl or benzyl;
R20 = H, CF3, 1-10C alkyl or benzyl;
R15 = H, 1-6C alkyl or benzyl; and
R16 = H or 1-4C alkyl.

ACTIVITY - Cytostatic; respiratory; antirheumatic; antiarthritic; osteopathic; cardiovascular; antiarteriosclerotic; ophthalmological; antiulcer; antiinflammatory; neuroprotective.

MECHANISM OF ACTION - Matrix metalloproteinase (MMP) inhibitor.

The potency of (I) as inhibitors of MMP-12 was measured using a fluorogenic substrate Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH2 (Mca, Dpa not defined) according to the procedure of C.G Knight et al., FEBS Lett., 296, 263-266 (1992). No Ki values for (I) are given.

USE - For inhibiting matrix metalloproteinase and the treatment of neoplasia, smoking-induced emphysema (claimed), cancer, rheumatoid arthritis, osteoarthritis, osteoporosis, cardiovascular disorders, atherosclerosis, corneal ulceration, dental diseases, gingivitis, periodontal diseases, neurological disorders, multiple sclerosis or inflammation.

Dwg.0/0

L18 ANSWER 4 OF 7 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1999:965640 SCISEARCH
THE GENUINE ARTICLE: 263RA
TITLE: The matrix metalloproteinase inhibitor BB-1101 prevents experimental autoimmune uveoretinitis (EAU)
AUTHOR: Wallace G R (Reprint); Whiston R A; Stanford M R; Wells G M A; Gearing A J H; Clements J M
CORPORATE SOURCE: GKT, DEPT OPHTHALMOL, ST THOMAS CAMPUS, LAMBETH PALACE RD, LONDON SE1 7EH, ENGLAND (Reprint); GKT, DEPT ACAD OPHTHALMOL, LONDON, ENGLAND; BRITISH BIOTECHNOL LTD, OXFORD OX4 5LY, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (DEC 1999) Vol. 118, No. 3, pp. 364-370.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 0009-9104.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB EAU is characterized by breakdown of the blood-retinal barrier and extravasation of leucocytes into retinal tissue leading to destruction of photoreceptor cells. Matrix metalloproteinases (MMP) have been implicated in trafficking of cells into tissues, but their role in inflammatory eye disease is unclear. A synthetic MMP inhibitor, BB-1101, was administered subcutaneously, from either day 0 or day 7, to Lewis rats challenged with bovine S-antigen to induce EAU. When given up to day 14, BB-1101 reduced the incidence of disease and delayed the day of onset of clinical disease. When administered from day 7 until day 21, EAU was completely abrogated. A quantitative polymerase chain reaction (PCR) assay showed an increase of both matrilysin (MMP-7), neutrophil collagenase (MMP-8) and macrophage metalloproteinase (**MMP-12**) in retinas from EAU animals compared with naive controls. These enzymes

are produced by activated leucocytes and act on components of the basement membrane. These results therefore implicate these MMP as integral to the development of pathology in EAU.

L18 ANSWER 5 OF 7 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1998:839652 SCISEARCH
THE GENUINE ARTICLE: 133EP
TITLE: Regional and differential expression of gelatinases in rat brain after systemic kainic acid or bicuculline administration
AUTHOR: Zhang J W; Deb S; Gottschall P E (Reprint)
CORPORATE SOURCE: UNIV S FLORIDA, COLL MED, DEPT PHARMACOL & THERAPEUT, TAMPA, FL 33612 (Reprint); UNIV S FLORIDA, COLL MED, DEPT PHARMACOL & THERAPEUT, TAMPA, FL 33612
COUNTRY OF AUTHOR: USA
SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (NOV 1998) Vol. 10, No. 11, pp. 3358-3368.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 0953-816X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Indirect evidence from in vitro studies implicates a functional role for matrix metalloproteinases (MMPs) in the central nervous system (CNS), including induction of neuronal migration during development and enhancement of neurite extension. Few reports have documented the expression of these enzymes in the brain, especially after injury in vivo. The objective of this study was to determine whether MMPs are expressed in various regional areas of rat brain after administration of the neurotoxin, kainic acid. Limbic motor seizures and neuronal degeneration were induced in Sprague-Dawley rats by systemic administration of kainate (10 mg/kg). Rats were subsequently divided into convulsive and non-convulsive groups, after observing their behaviour in response to the drug. Animals were killed 6, 12, 24, 72 and 168 h (7 days) after injection of kainate. Gelatinases were extracted from various brain regions and assayed by gelatin-substrate zymography. Levels of glial fibrillary acidic protein (GFAP) in corresponding regions were measured by ELISA. In the absence of treatment, MMP-2 and MMP-9 activities were expressed differentially in various brain regions with the highest levels in the hippocampus and the lowest in the cerebellum. In areas from convulsive rats, MMP-9 activity was markedly elevated at 6 h, and reached a maximum at 12 h after injection of kainate (8.1-fold hippocampus, 7.7-fold diencephalon, 7.2-fold striatum, 5.7-fold

frontal cortex, 5.5-fold cerebellum, 2.6-fold midbrain). MMP-2 activity was induced more than two-fold in the hippocampus, diencephalon and striatum, to a lesser extent in the frontal cortex and midbrain, and was unchanged in the cerebellum, 72 h after injection. Neither MMP activity was altered in any brain region derived from non-convulsive rats. Treatment with the GABAA antagonist, bicuculline, resulted in increased levels of **MMP** -9, **12** h after drug administration, but no change in levels of MMP-2 up to 3 days following treatment. GFAP levels were induced 3 days after kainic acid injection in brain regions where MMP-2 was elevated. Nissl staining displayed the classical, regional neurodegeneration in kainate-treated animals that exhibited seizures. No obvious degeneration was detected in kainate-treated, non convulsive rats or bicuculline-treated animals. These data demonstrate that MMP-9 and MMP-2 are differentially expressed with respect to time after kainic acid injection, and suggest that they are regulated by convulsion and/or neurodegenerative-associated mechanisms, respectively. Although similar in catalytic activity, MMP-9 and MMP-2 may play different roles in response to kainic acid-induced seizure and neuronal degeneration.

L18 ANSWER 6 OF 7 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998333921 MEDLINE
DOCUMENT NUMBER: 98333921 PubMed ID: 9670846
TITLE: Matrix metalloproteinase expression in an experimentally-induced DTH model of **multiple sclerosis** in the rat CNS.
AUTHOR: Anthony D C; Miller K M; Fearn S; Townsend M J; Opdenakker G; Wells G M; Clements J M; Chandler S; Gearing A J; Perry V H
CORPORATE SOURCE: The CNS Inflammation Group, Department of Pharmacology, University of Oxford, UK.. daniel.anthony@pharm.ox.ac.uk
SOURCE: JOURNAL OF NEUROIMMUNOLOGY, (1998 Jul 1) 87 (1-2) 62-72.
Journal code: HSO; 8109498. ISSN: 0165-5728.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ED Entered STN: 19980820
Last Updated on STN: 20000303
Entered Medline: 19980813

AB In an experimentally-induced DTH model of MS, we examined mRNA and protein expression of a range of MMPs and of TNFalpha to establish the contribution that individual MMPs might make to the pathogenesis. In control rat brain, mRNA for all of the MMPs

examined was detectable. However, by immunohistochemistry, only MMP-2 could be detected. In the DTH lesions, significant increases in the level of mRNA expression were observed for MMP-7, **MMP** -8, **MMP-12**, and TNFalpha. Where expression of MMP mRNA was increased, there was a corresponding increase in protein expression detected by immunohistochemistry. To determine whether the upregulated MMPs could invoke destructive events in the CNS, highly purified activated MMP-7, MMP-8, and MMP-9 were stereotaxically injected into the brain parenchyma. All provoked recruitment of leukocytes and BBB breakdown. In addition, MMPs 7 and 9 induced loss of myelin staining. In conclusion, specific MMPs are upregulated in DTH lesions; for the most part, measurement of mRNA was a predictor of increased protein expression. From our injections of MMPs, it is clear that the upregulated MMPs in the DTH lesions could participate in the disruption of the BBB, leukocyte recruitment, and tissue damage.

L18 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:308221 BIOSIS
DOCUMENT NUMBER: PREV199699030577
TITLE: Macrophage metalloelastase (**MMP-12**) degrades matrix and myelin proteins.
AUTHOR(S): Chandler, S.; Lury, J.
CORPORATE SOURCE: Neures Limited, 4-10 The Quadrant, Barton Lane, Abingdon, Oxon OX10 9DR UK
SOURCE: FASEB Journal, (1996) Vol. 10, No. 6, pp. A1129. Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

FILE 'CAPLUS' ENTERED AT 14:50:56 ON 23 APR 2001
L19 14 SEA FILE=CAPLUS ABB=ON PLU=ON (MACROPHAGE(W)(METALLOELASTASE OR METALLO ELASTASE))(2A)12
L20 0 SEA FILE=CAPLUS ABB=ON PLU=ON L19 AND (MS(S)SCLER? OR MULTIPLE SCLER?)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 14:51:55 ON 23 APR 2001)
L21 1 S L20
L22 0 S L21 NOT (L8 OR L17)

FILE 'HOME' ENTERED AT 14:52:38 ON 23 APR 2001